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1. Enantioselective deprotonation reactions of (arene)tricarbonylchromium complexes, and 2. Reductive lithiation of (arene)tricarbonylchromium acetals.

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1. Enantioselective Deprotonation Reactions of (Arene)tricarbonylchromium Complexes

2. Reductive Lithiation of (Arene)tricarbonylchromium Acetals

by

Michael John Siwek

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ABSTRACT

Chapter 1

Chiral alkyllithium bases are able to selectively lithiate either the pro R or pro S ortho site of several monosubstituted η^6-(arene)tricarbonylchromium (0) complexes. The chiral alkyllithium bases were prepared from the corresponding chloride using the radical anion, lithium 4,4'-di(*tert*-butyl)biphenyl (LiDBB). The base derived from 8-phenylmenthol provided the highest degree of asymmetric induction in [η^6-(dimethoxymethyl)benzene]tricarbonylchromium (0) with a respectable chemical yield.

Chapter 2

η^6-(Arene)tricarbonylchromium (0) acetal complexes can be reduced at low temperatures by the radical anion, LiDBB, to generate the corresponding benzyllithium complexes. Once formed, these benzyllithium complexes can trap a variety of electrophiles to give benzyl-functionalized chromium complexes in good yields. In addition, the reduction of an ortho substituted complex, and subsequent trapping with an electrophile occurs with a high degree of diastereoselectivity

Here had he built his refuge, being a little weary; not disgusted, for the large aversions are unknown to the sage; but a little weary of interrogating men, whose answers to the only interesting questions one can put concerning nature and her veritable laws are far less simple than those that are given by animals and plants.

-Maurice Maeterlinck, *The Life of the Bee*

DEDICATION

This thesis is dedicated to my girlfriend Shannon, who has given me a few good smacks whenever the need arises, and secondly to Tasha, who never fails to sniff out something for me to shoot.

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Over the last year especially I have come to know a small group of exceptional people quite well, and these folks certianly deserve my utmost thanks for tolerating the delusions which sometimes overtake me. These people are; Anne (dances with vampires) Charlton, Nikki (are you behaving yourself) Fransen, Kevin (naked) M^{c}Kay, Jay (I'm gonna kill someone) Kiser and Ed (this one is best left unsaid) Brnardic.

I also am grateful for the help and guidance that my boss Jim has given me, and I must say that for a self proclaimed moderate left winger, he still displays admirable right wing qualities.

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LIST OF ABBREVIATIONS

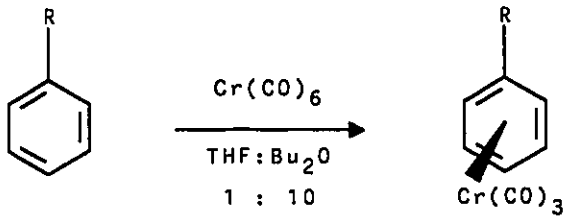
*n*BuLi	*normal*-butyllithium
*sec*BuLi	*secondary*-butyllithium
*t*BuLi	*tertiary*-butyllithium
°C	degrees Celsius
CH_2Cl_2	methylene chloride
cm^{-1}	wavenumbers
δ	chemical shift
de	diastereomeric excess
DMSO	dimethylsulfoxide
ee	enantiomeric excess
e^-	electron
Et_2O	diethyl ether
equiv	equivalents
g	grams
h	hours
IR	infrared
LDA	lithium diisopropylamide
m	multiplet (NMR)
M	molarity
MHz	megahertz

mL	millilitres
mmol	millimole
MS	mass spectrometry
mp	melting point
NMR	nuclear magnetic resonance
Ph	phenyl
ppm	parts per million
q	quartet (NMR)
s	singlet (NMR)
t	triplet (NMR)
THF	tetrahydrofuran
TLC	thin layer chromatography

Chapter 1: The Enantioselective Deprotonation Reactions of (Arene)tricarbonylchromium Complexes

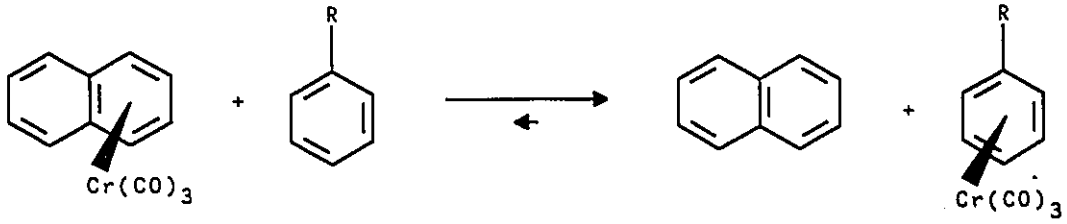
Introduction

The use of (arene)tricarbonylchromium(0) complexes in organic synthesis has been an expanding area of interest in recent years.[1] An arene chromium complex can be prepared by refluxing the arene and $Cr(CO)_6$ in a solution of dibutyl ether and THF.[2] Thermolysis with $Cr(CO)_6$ is by far the most common method employed to date (**Scheme 1**).



Scheme 1

Alternatively, the equilibrium which exists between a complexed arene and a free arene can be exploited to yield the more stable complex. For this purpose (naphthalene)tricarbonylchromium(0) can be utilized since this complex tends to be unstable and will yield the chromium complex of the arene with which it is stirred (**Scheme 2**).[3]



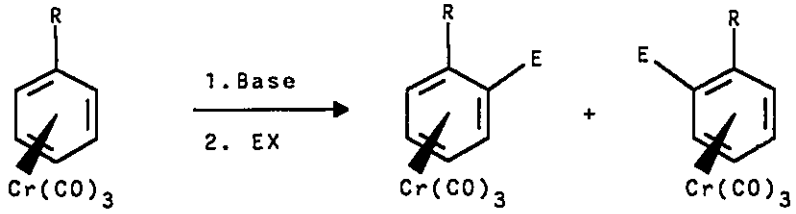
Scheme 2

The attention which these compounds have created evokes little surprise when the consequences of complexing an arene to chromium are realized. Consider; i) the enhanced acidity of arene protons, ii) the enhanced acidity of benzylic and homobenzylic protons, iii) the enhanced rate of solvolysis of benzylic and homobenzylic leaving groups, iv) the decreased ability of the arene ring to undergo electrophilic substitution, with a concomitant increased ability for nucleophilic substitution, and v) the asymmetric induction by the chromium tricarbonyl moiety.[4]

Of particular interest are the first and final mentioned consequences, i) and v), which when utilized in conjuction with each other provide a broad spectrum of synthetic possibilities. Upon complexation of the arene to chromium, a decrease of 6-7 pK_a units of the arene protons is observed,[5] as well as the destruction of the plane of symmetry which contains the arene ring.[6] The implication of this is twofold; 1) metallation of the arene ring becomes much more facile, and 2) a ring carbon can be rendered chiral.

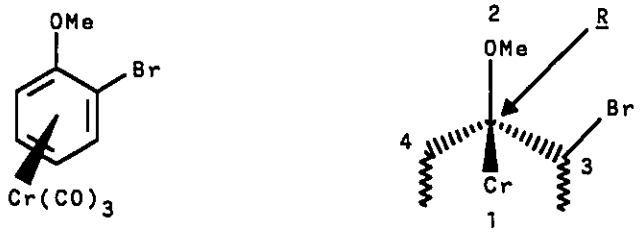
Metallating arene chromium complexes has received enough attention so as to have become a common procedure which works in wide variety of cases.[7] An illustration of a general metallation reaction, which yields in this case a pair of enantiomers is given in **Scheme 3**. With respect to which bases can be employed, ^{n}BuLi, MeLi, ^{t}BuLi,[8] LiTMP[9]

and numerous chiral lithium amides[10,11] have all successfully metallated various arene chromium complexes in respectable yields. The increase of acidity in the complexed arene protons is not only evident by pK_a, but is also evidenced in a kinetic fashion. Bases such as ^{sec}BuLi and ^{t}BuLi are capable of metallating free arenes,[12] but this occurs generally at a much slower rate than for the complexed arene.



Scheme 3

That the products in **Scheme 3** are in fact enantiomers is difficult to see since the chiral centers in these complexes are not of the classical tetrahedral geometry. Upon further inspection it becomes apparent that the two structures are nonsuperimposable mirror images and each of the substituted arene carbons can be thought of as tetrahedral (**Scheme 4**). To assign R and S descriptors, the same method used for classical chiral carbons is applied; thus the arene carbon bearing the methoxy group, (**Scheme 4**), would be designated R.



Scheme 4

Obtaining specifically one enantiomer of an arene complex opens up many synthetic routes to enantiomerically pure compounds. An example of such use is the asymmetric synthesis of dihydroisocoumarins, which was carried out by Green et al (**Figure 1**).[13] By protecting benzaldehyde with a diol derived from (+)-diethyl tartrate, and complexing the resulting acetal to chromium (**1**), the pro-R ortho site was selectively methylated with a de of 92%. The resulting mixture of diastereomers was easily separated by chromatography, at which point the major stereoisomer was then lithiated at the benzylic position and treated with the appropriate Weinreb amide[14] to yield the ketone **2**. Subsequent reduction with DIBAL-H yielded a diastereomeric mixture **3** and **3'**, with de's from 74% to 96%. The major diastereomer was again separated through chromatography and subjected to acidic conditions and oxidation to yield the corresponding dihydroisocoumarin **4**, in up to 83% yield.

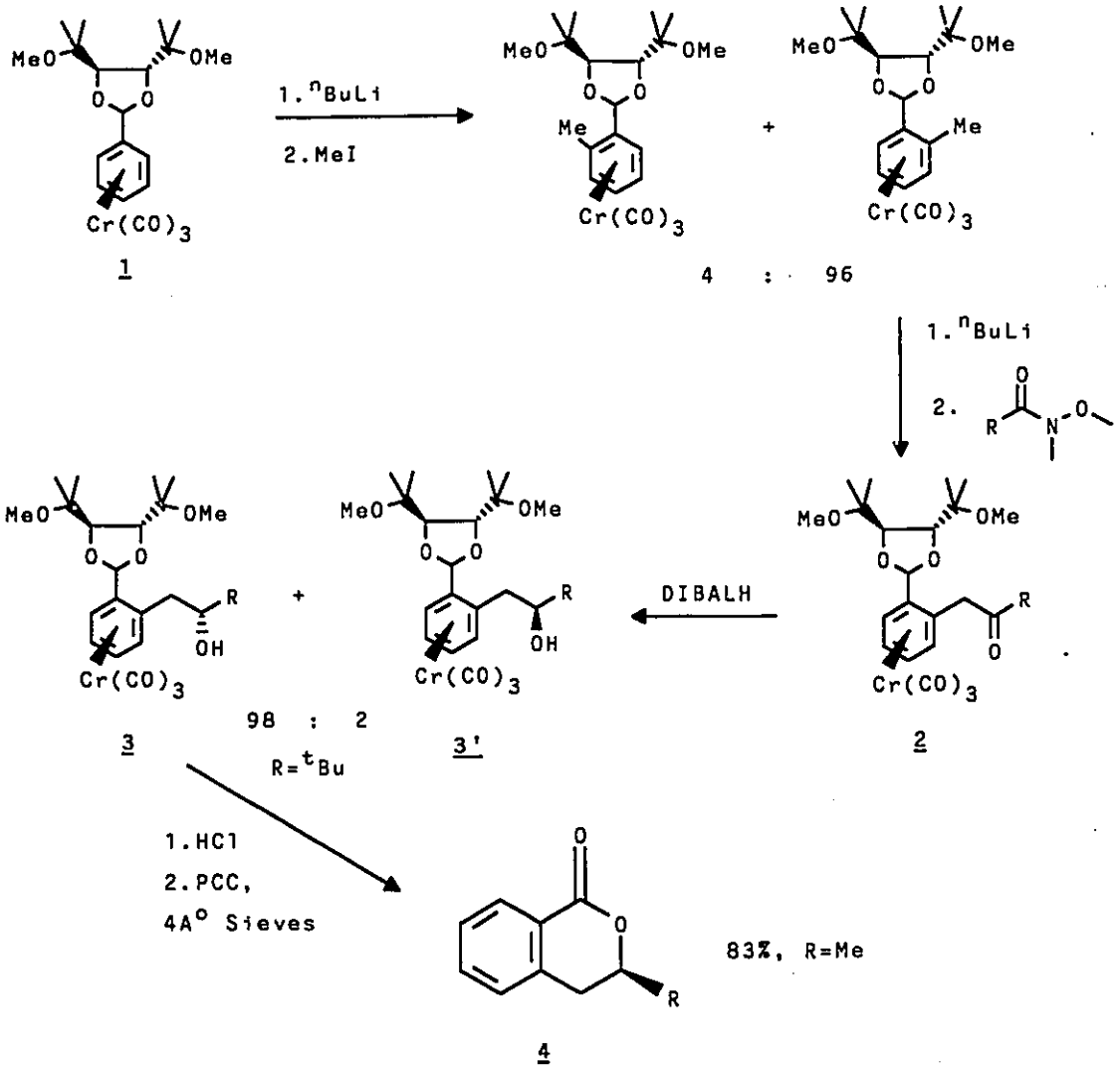
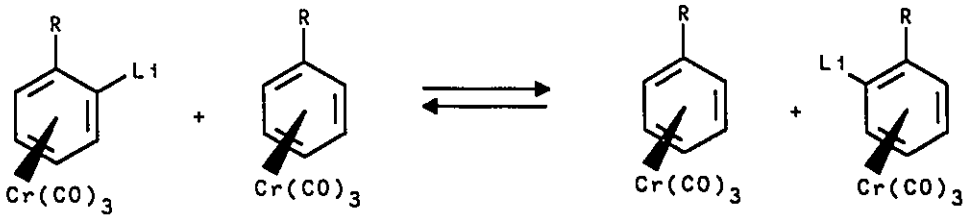


Figure 1: Synthesis of dihydroisocoumarins

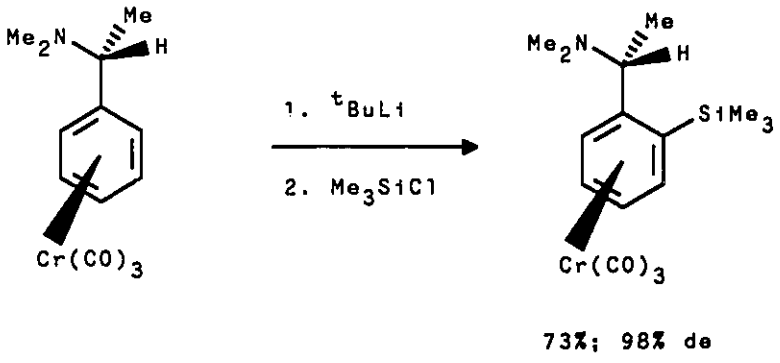
It is important to note that in this particular chemistry[8] rapid addition of base results in kinetic lithiation, and upon warming, the lithiated species equilibrates. The equilibration of the lithiated species can occur through a number of routes, the most plausible of which

is shown in **Scheme 5**, while other routes involving a perlithiated species cannot be ruled out.



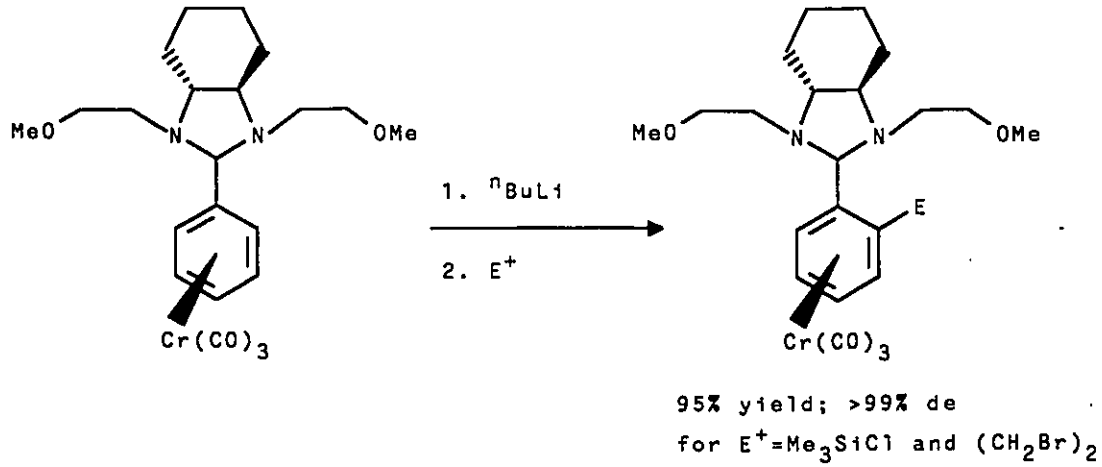
Scheme 5

There exists a fair amount of research which utilizes a chiral auxilary on (arene)tricarbonylchromium (0) complexes. Previous work by Davies and Heppert saw the use of α-amino auxilaries to carry out highly diastereoselective ortho metallation (**Scheme 6**).[15] Despite the high levels of diastereomeric induction, the auxilaries tended to be very difficult to remove, thus rendering this methodology somewhat impractical.



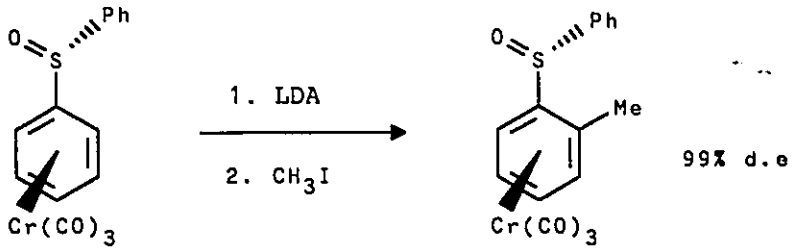
Scheme 6

In keeping with a protected benzaldehyde chromium complex, Alexakis et al were able to make a variety of aminals of benzaldehyde chromium complexes.[16] These were then ortho lithiated and quenched with a few electrophiles to give corresponding products in very high yields and high de's (**Scheme 7**).



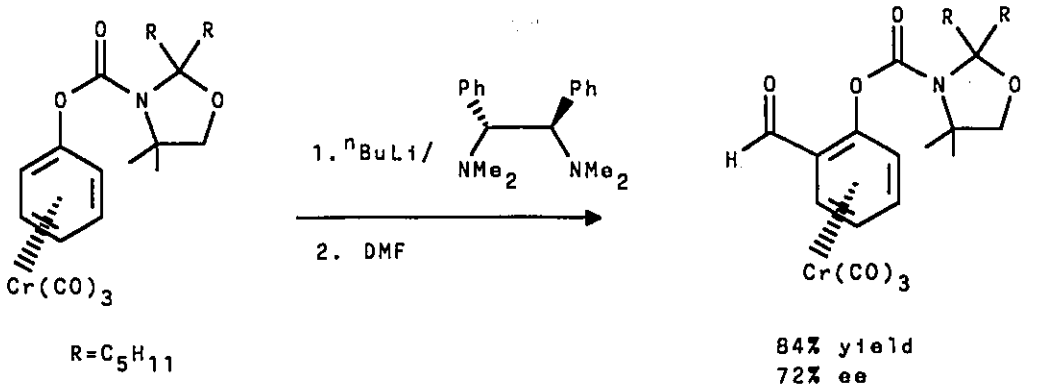
Scheme 7

A new approach for a chiral auxiliary was taken by Davies and coworkers.[17] It involved the use of a phenyl sulfoxide substituent on the arene ring of a chromium complex. Using this approach the authors were able to lithiate this sulphoxide and trap with CH_3I to give the ortho-functionalized product in 36% yield but with a de of 99% **(Scheme 8)**.



Scheme 8

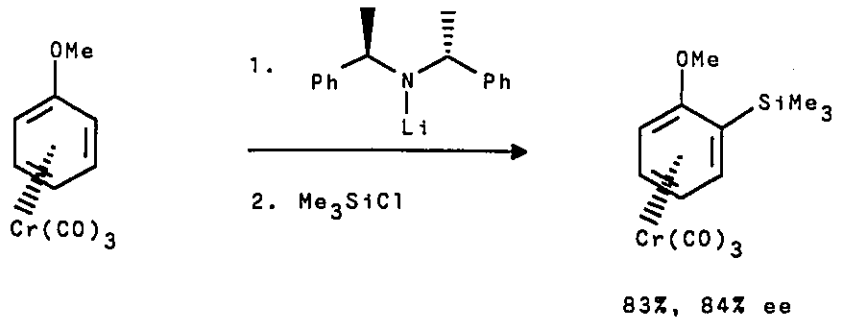
A second way to introduce a new stereogenic center is to simply have it present as a chelating agent for an achiral base. Uemura et al were able to lithiate a variety of phenylcarbamate chromium complexes in the presence of several chiral diamines and quench with electrophiles to give optically active products in up to 82% ee (**Scheme 9**).[18]



Scheme 9

Aside from having a stereogenic center in the substrate itself, a base containing such a center can be employed to selectively lithiate arene chromium complexes. Simpkins et al utilized a chiral lithium amide to selectively metallate an anisole chromium complex and

trap with Me_3SiCl to yield the corresponding product in 83% yield with 84% ee (**Scheme 10**).[11] That these chiral lithium amides were able to induce a respectable level of asymmetry is not surprising, since they have received widespread attention recently in numerous reactions.[19]



Scheme 10

Once metallation of an achiral complex with a chiral base has taken place, the lithiated species are enantiomers, unlike the diastereomeric aryllithium complexes formed with covalently attached chiral auxiliaries (**Figure 1, Schemes 6-8**). The reasoning for the discrimination of ortho sites stems from the transition states in the deprotonation reaction. When the base containing the stereogenic center initiates the metallation, its presence immediately renders the arene carbon chiral, thus forming diastereomeric transition states. **Figure 2** illustrates this for a general case where the base contains a chiral center whose configuration is S.

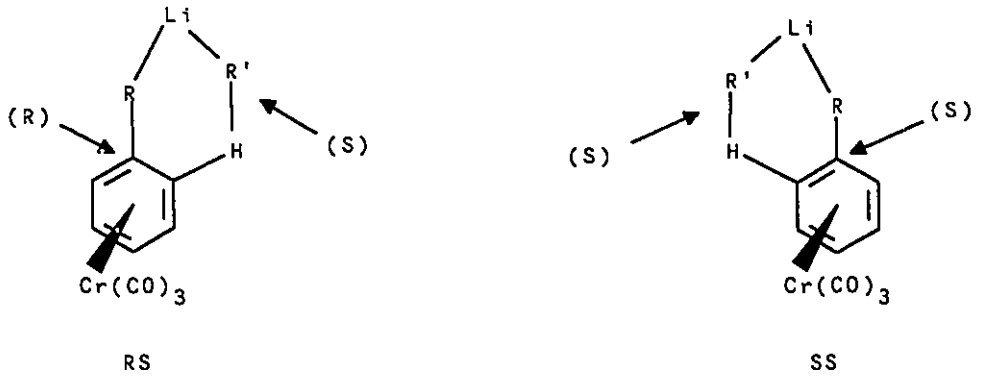
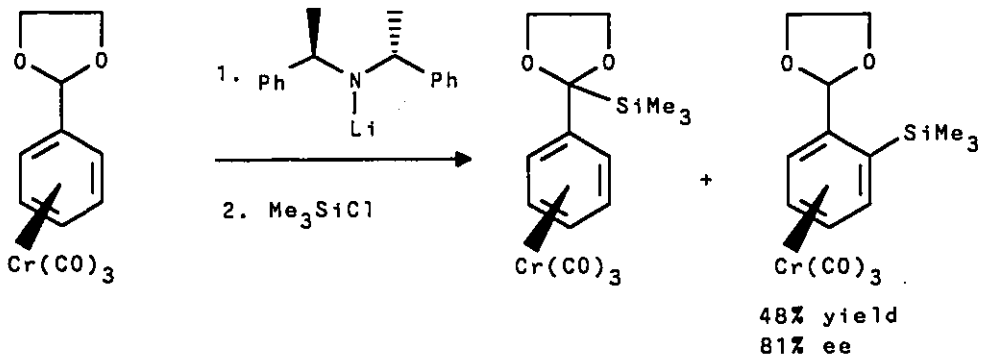


Figure 2: Transition state models

The control of stereochemistry under these conditions is one of kinetics, stemming from the energy difference of the diastereomeric transition states. This control may work well, as was demonstrated above by Simpkins, but the problem inherent to this approach is the loss of stereochemical integrity of the lithiated species through the same equilibrating process as described by Green (**Scheme 5**). Electrophiles other than Me_3SiCl gave poor yields of racemic products, indicating that the metallation was not going to completion and that the small amounts of lithiated species which were present were equilibrating. Further investigation showed that the anisole system requires 3 h to be completely metallated by the chiral lithium amide, thus giving ample time for the lithiated species to racemise. In addition, experiments also showed that the lithiated anisole complex is configurationally stable, thus indicating that a loss of stereochemical integrity occurs only in the presence of the undeprotonated complex. Respectable results were obtained with Me_3SiCl due to its ability to be used in the presence of the amide base, and because it liberates LiCl, which increases the reaction rate dramatically (thus minimizing the racemisation). With this in mind the anisole complex was then metallated in the presence of LiCl, and other

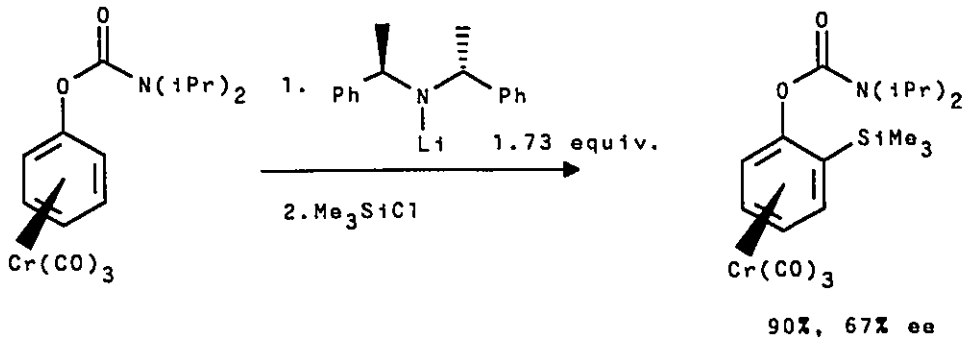
electrophiles were then shown to give greatly improved results. Benzaldehyde, for instance, gave the corresponding product in 67% yield with an ee of 65%.

Chromium complexes other than that of anisole have been treated with chiral lithium amide bases.[9] Kundig et al conducted studies similiar to Simpkins, employing a cyclic acetal substrate (**Scheme 11**). This acetal exhibited a tendency to lithiate the benzylic site, but the ortho product obtained was found to have an ee of 81%.



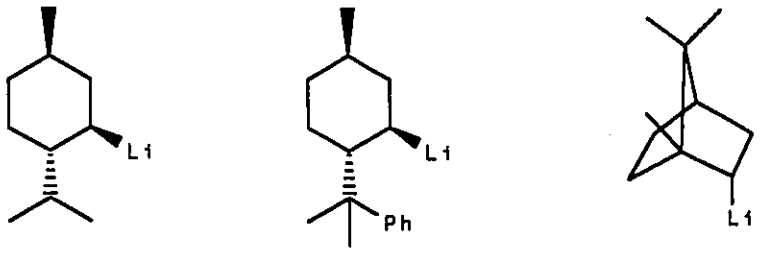
Scheme 11

Further investigations by Kundig involved the use of a phenyl carbamate complex for deprotonation reactions (**Scheme 12**). Oddly enough, the chiral amide base employed failed to give optically active products when used in equimolar quantities. Upon increasing the amount of base to 1.73 equivalents, the enantiomeric excess improved to 67%.



Scheme 12

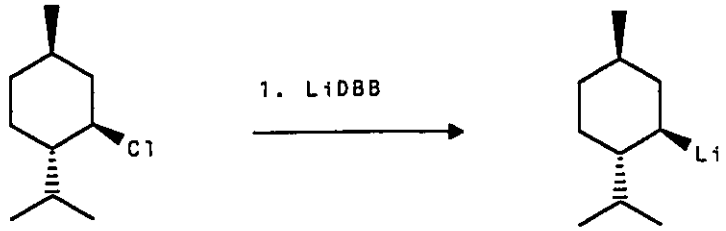
It has become evident that an important series of experiments would involve the use of chiral alkyl lithium bases to selectively deprotonate various chromium complexes. The pK_as of these bases would be approximately the same as the pK_a of ^{sec}BuLi , which has a pK_a value of ca. 51.[20] With a pK_a of this magnitude, compounds other than chromium complexes, such as ferrocenes and biphenyl systems, could be deprotonated and subsequently trapped with electrophiles. Three chiral alkyl lithium bases which would be good candidates are shown in **Figure 3**.



5 6 7

Figure 3: The three bases for this study

The challenge involved with chiral alkyl lithium bases is to make them in enantiomerically pure form. The traditional method of treating the corresponding chloride with 2% sodium-lithium sand is exceedingly unattractive due to low yields of the alkyl lithium species, and difficulty of the preparation for the lithium sand.[21] An alternative method would involve the use of a radical anion, such as lithium 4,4'-di(*tert*-butyl)biphenyl (LiDBB), to lithiate the corresponding chloride (**Scheme 13**).



Scheme 13

Freeman has shown that lithiation of many alkyl halides could be achieved in seconds through the use of this method.[22] An important aspect of the systems chosen is the stereochemistry of the carbon bearing the lithium. Once lithiation has taken place, the carbon bearing the lithium atom is susceptable to rapid epimerization, which is governed by an equilibrium. Maercker et al[23] found that menthyllithium (5), equilibrates to a 15:1 ratio where the lithium is in an equatorial position. Maercker also found that bornyllithium (7), equilibrates to a 96:4 ratio where the lithium is endo. It is not known if this center is even the primary source for the discrimination of the prochiral proton abstraction. The spatial orientation of any of the adjacent chiral centres or a synergystic combination of all the chiral centres in these bases may be responsible for any enantioselective

deprotonations observed. The wide variety of aggregation modes which is possible for alkyllithium bases, and the difficulty of applying any such knowledge to transition states makes any definitive statements difficult.

Thus, for **Chapter 1** of this thesis, a variety of monosubstituted (arene)tricarbonylchromium complexes were deprotonated by the three chiral bases shown in **Figure 3** and trapped by a number of electrophiles with the expectation of obtaining a high enantiomeric excess in the product.

Results and Discussion

To carry out the intended asymmetric lithiations, some prochiral substrates were chosen (**Figure 4**).

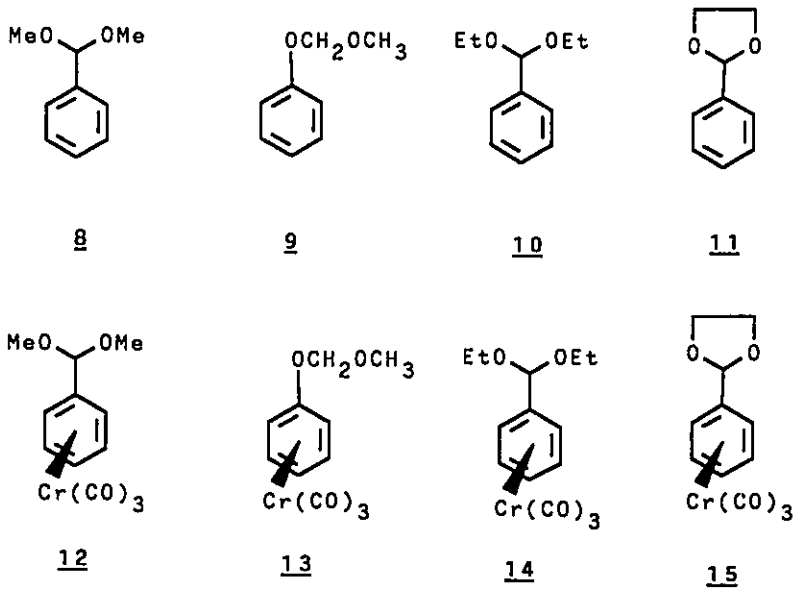
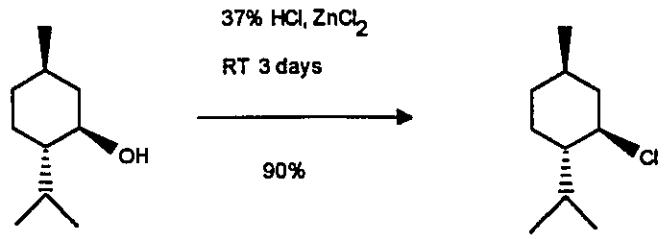


Figure 4: Substrates for deprotonations (12-15) and their precursors (8-11)

These were chosen for their ease of preparation and for their useful protected functionality. Each of the dimethyl (**8**), diethyl (**10**) and cyclic (**11**) acetals were prepared from benzaldehyde, pTsOH and their corresponding alcohol, while the MOM protected phenol (**9**), was made from phenol, NaOH and chloromethyl methyl ether. Once these were prepared, thermolysis with $Cr(CO)_6$ yielded the above complexes in yields of 73% (**12**), 85% (**14**), 74% (**13**), and 83% (**15**). Complexations of arenes which have simple functionality typically give yields in the 80-90% range,[2] but due to the ease of preparation

of 12, 13, 14, and 15 in large quantities, no attempts to optimize the complexation yields were made.

(-)-Menthyl chloride (17), was synthesized from (-)-menthol (16), by a modification of the literature procedure (**Figure 5**). The orginal preparation called for treatment of (-)-menthol with $ZnCl_2$ and HCl for 5 h at 35 °C[24], but the conditions actually employed were room temperature and three days, which gave much cleaner product.



16 17

Figure 5: Preparation of (-)-menthylchloride

The synthesis of 2-bornyl chloride (20), which was derived from (+)-camphor (18), (**Figure 6**), met with some unexpected results. Reduction of the ketone function by $LiAlH_4$ was carried out in Et_2O at reflux, to give a mixture of (+) and (-)-isoborneol (19). A more selective reduction has been reported to occur at low temperature, affording (-)-isoborneol with little contamination.[25] A polarimeter was not available at the time 19 was prepared, so this problem of enantiomeric purity could not be addressed at that point. In any event, the optical rotation later showed that there was an excess (52% ee), of (-)-isoborneol, so there was still a chance to obtain the corresponding chloride (20) with some enantiomeric excess.

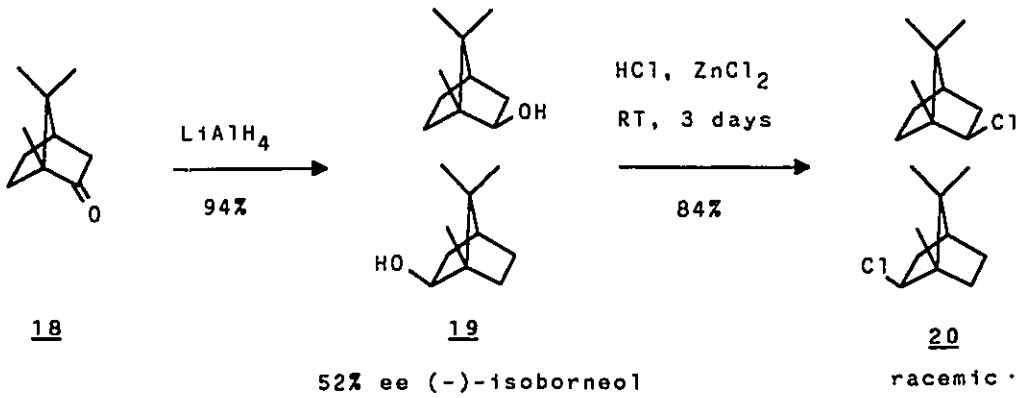
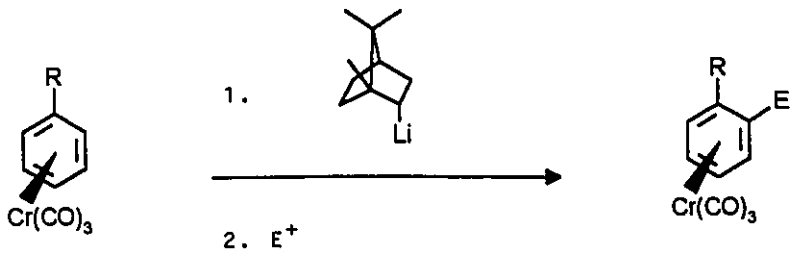


Figure 6: Preparation of 2-bornylchloride

The chlorination of **19**, yielded a racemic mixture of bornyl chloride (**20**) in our hands. Again, without a polarimeter, the chloride was not known to be a racemic mixture of enantiomers and the subsequent lithiation and deprotonation reactions were carried out (**Scheme 14**) with, (obviously), poor stereochemical results. That bornyl chloride was in fact made is evidenced by the melting point which was found to be 131-132 °C, matching the literature value of 131-132 °C.[26] Isobornyl chloride has a melting point of 147 °C which is quite different from that of bornyl chloride so there is no confusion as to which chloride was prepared. The best method for preparing optically pure bornyl chloride would have been to bubble HCl gas through a solution of α-pinene and pentane.[26] This method was overlooked because of the ease with which the (-)-menthyl chloride (**17**) was prepared and as a result the same pathway used for it was applied in making bornyl chloride. In addition, the other two bases **5** and **6**, gave such respectable results in the deprotonation reactions that further attempts to make **7** in enantiomerically pure form were not carried out.

The lithiation reaction for 2-bornyllithium is shown in **Scheme 14**. Complexes **12** and **13** were carried through this reaction a number of times where Me_3SiCl was the electrophile. The best yields for those reactions were 60-80%, but the ee's were 0%, for reasons discussed above.



Scheme 14

The preparation of "8-phenylmenthyllithium" (**6**) began with the synthesis of chloride **21**, which in turn was prepared from 8-phenylmenthol (**Figure 7**).[27] In this case, the chlorination proceeded more cleanly in the presence of neat $SOCl_2$, giving **21** in 82% yield, as opposed to the $ZnCl_2$/HCl protocol employed previously for the preparation of **17** (50% yield).

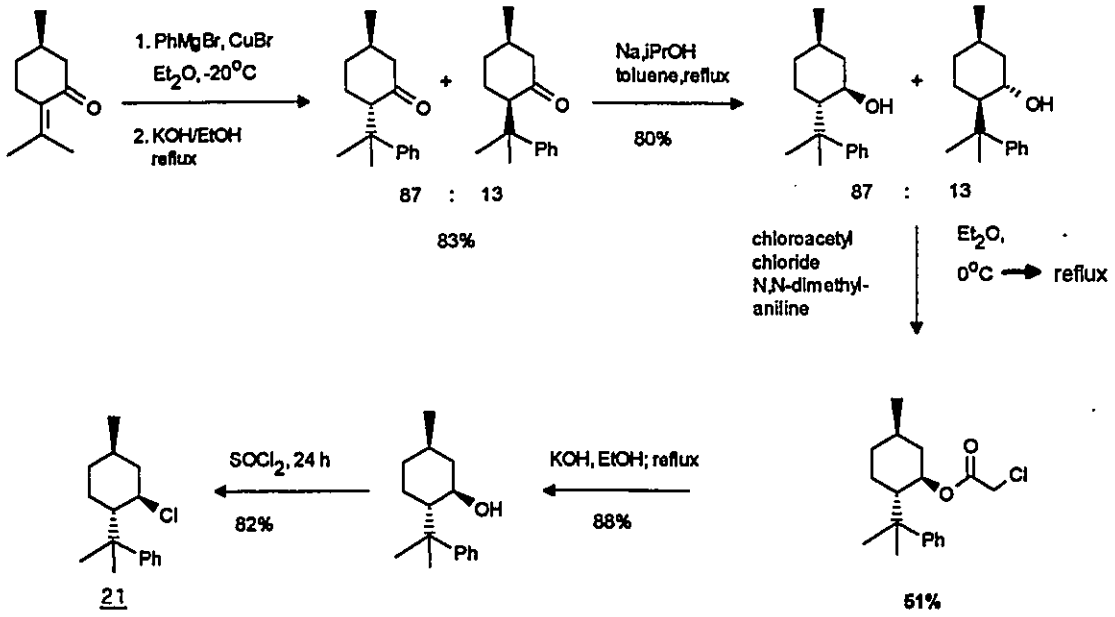
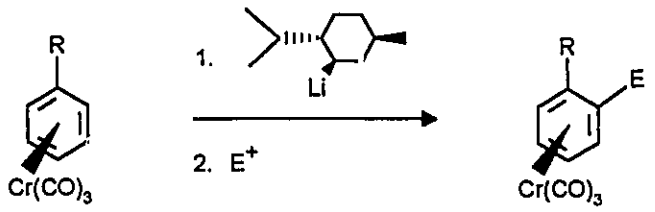


Figure 7: Preparation of 8-phenylmenthylchloride

In order to carry out the deprotonation reactions the actual alkyllithium species had to be prepared by treating the corresponding chloride with the radical anion LiDBB. The preparation of a solution of LiDBB had poor reproduceablility when its literature preparation was followed.[22] The most successful protocol involved a sizeable piece of lithium metal (dime size), which was scratched with two syringe needles in the solution of THF and DBB. At this point the deep blue-green colour of the radical anion could be seen streaming off the lithium metal. It certainly seems evident that the main obstacle to overcome in the formation of LiDBB is to provide a fresh metal surface and to achieve this by any means necessary. The three chlorides utilized (17, 20, 21), all reacted with LiDBB in much the same fashion, as expected on the basis of Freeman's literature report.[22]

The results for the reaction involving (1R, 2R, 5R)-menthyllithium (5) (**Scheme 15**), are given in **Table 1**, while structures for all the reaction products are given in **Figure 8**.



Scheme 15

Table 1: Menthyllithium Results

Entry	*Complex*	*Method*	*Electrophile*	*Product(s)*	*Yield (%)*	*ee (%)*
1	**12**	C	Me_3SiCl	**22**	85	35
2	**12**	D	Me_3SiCl	**22**	57	70
3	**12**	C	CH_3I	**23**	10 (65)	14
4	**12**	D	CH_3I	**23**	61 (76)	56
5	**12**	C	$(CH_3)_2S$	**23**	51 (81)	30
6	**12**	C	PhCHO	**24**	26; 24 *	30
7	**12**	D	PhCHO	-	failed	NA
8	**12**	C	Acetone	**25**	71	+4.6 **
9	**12**	E	Me_3SiCl	**22**	38 (45)	32
10	**13**	C	Me_3SiCl	**26**	81	32
11	**13**	D	Me_3SiCl	-	failed	NA
12	**13**	C	CH_3I	**27**	13 (75)	15
13	**13**	D	CH_3I	**27**	10 (90)	40
14	**14**	C	Me_3SiCl	**28**	71 (83)	30
15	**14**	D	Me_3SiCl	-	failed	NA
16	**15**	C	Me_3SiCl	**30**	72%***	NA

Method C: half hour metallation time, THF as solvent; **Method D**: half hour metallation time, 4:1 Et_2O:THF as solvent; **Method E**: 10 min. metallation time, THF as solvent.
* yields for diastereomer #1 and #2 respectively; ** $[\alpha]$ (c 0.38, CH_2Cl_2); *** $SiMe_3$ in the benzylic position.

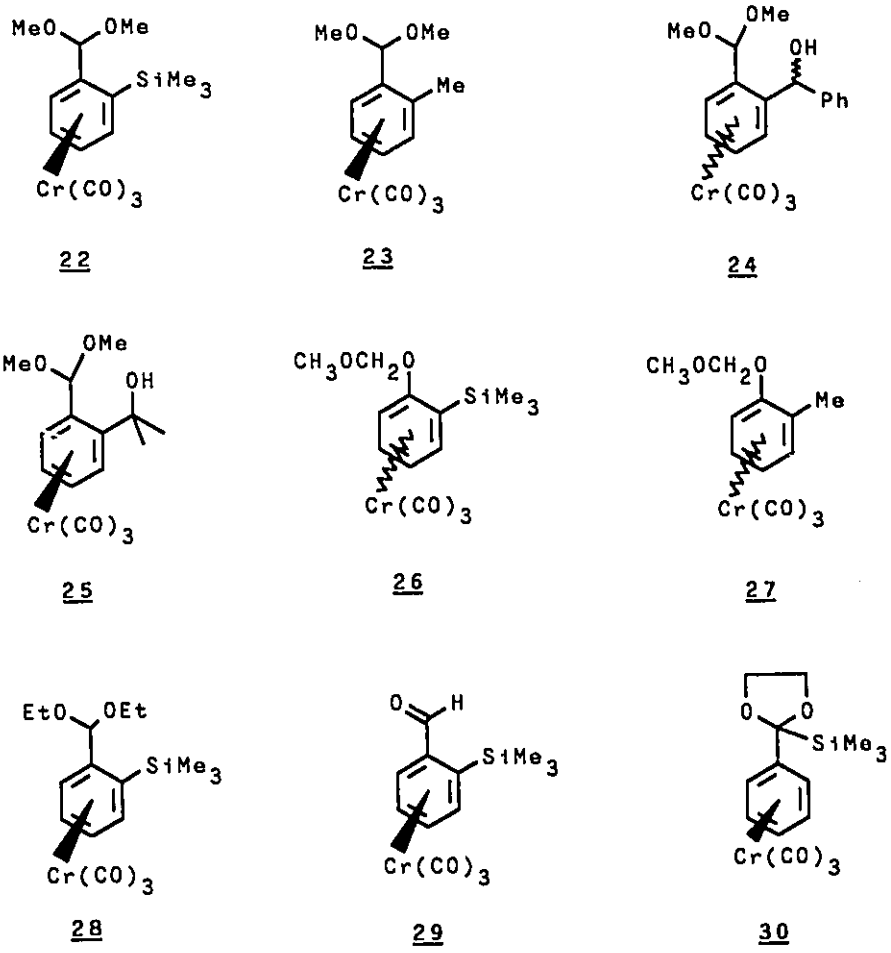


Figure 8: Lithiation Products

To determine the enantiomeric excess (ee) of the lithiation products, the ^{1}H NMR spectrum of the sample was obtained in the presence of the chiral lanthanide shift reagent Eu(hfc)$_3$. In the majority of cases, the spectra displayed separation of some resonances for the enantiomers, and simple integration then revealed the enantiomeric excess. This protocol was unsuccessful for a small number of substrates (**24 diastereomer #2**, **25**, **28**,); **28**, however, could be hydrolyzed to the corresponding aldehyde (**29**), which worked well with the shift reagent. Acetylating the alcohol functions of the remaining compounds **24**

and **25**, may be a possible way to obtain an accurate ee measurement, but this transformation did not prove successful.

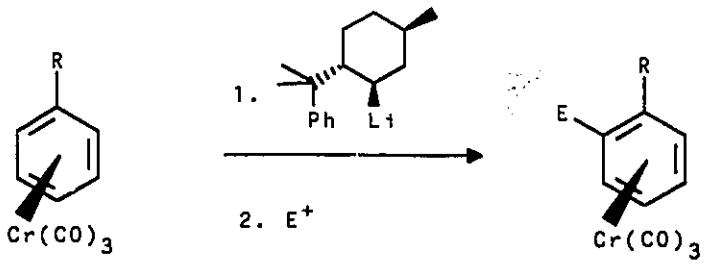
Initial lithiation/functionalization reactions were performed with menthyllithium (**5**), and substrates **12**, **13**, **14** in THF, with electrophilic quenching of the aryllithium with Me_3SiCl in THF solvent (**Table 1**, entries 1, 10, 14). Several repetitions of each lithiation gave respectable chemical yields (70-85%), and modest, but significant asymmetric induction (30-35% ee). Other electrophiles, such as CH_3I and PhCHO, were introduced only very sluggishly under identical conditions (entries 3, 6).

Altering the solvent had a dramatic effect on the asymmetric induction in the products (entries 2, 4, 17). This occurred, however, at the expense of chemical yield, and in some instances halted the reaction completely (entries 7, 11, 13, 15). The actual solvent system utilized consisted of Et_2O and THF in a 4:1 ratio, due to the inability of the radical anion to form in pure ether.[22] To circumvent this problem, the LiDBB was prepared in 3 mL of THF, followed by the addition of 12 mL of Et_2O. Attempts to prepare the alkyllithium base and then evaporate the THF, in order to later add solely ether, failed.

An indication as to the nature of the lithiated complex is given by the results provided when acetone was employed as the electrophile (entry 8). The fact that very little starting material was recovered and a respectable 71% yield for the reaction was obtained shows that the lithiated complex is acting primarily as a nucleophile and not as a base. This opens up possibilities for other carbonyl functional groups where there are α-hydrogens present, such as other ketones, aldehydes and even esters. If these electrophiles could be

used with some success, this would dramatically increase the usefulness of this methodology.

After having worked with menthyllithium for a substantial length of time, and observing no further increase in the asymmetric induction, 8-phenylmenthyllithium (6), was employed. This particular species was chosen due to its remarkable ability to induce high levels of asymmetry in Ene reactions.[28] Lithiation of 12 with 8-phenylmenthyllithium (6), and trapping with Me_3SiCl gave a good yield of 22 (77%), and an 80% ee. This result was very encouraging since the highest ee value to date was 84%.[11] It is worth pointing out that in this instance the opposite enantiomer is in excess, and thus by utilizing either base 5 or 6, both enantiomers can be obtained in excess. Benzaldehyde also worked reasonably well (**Table 2**, entry 6), but the enantiomeric excess of the second diastereomer (24) could not be obtained as was the case with menthyllithium (**Table 1,** entry 6).



Scheme 16

Table 2: 8-Phenylmenthyllithium Results

Entry	*Complex*	*Method*	*Electrophile*	*Product(s)*	*Yield (%)*	*ee (%)*
1	**12**	A	Me_3SiCl	**22**	77	80
2	**12**	B	Me_3SiCl	**22**	74	54
3	**12**	A	CH_3I	**23**	21 (91)	73.5*
4	**12**	A	acetone	**25**	failed	NA
5	**12**	A	Me_2S	**23**	failed	NA
6	**12**	A	PhCHO	**24**	43; 30	60; ?
7	**13**	A	Me_3SiCl	**26**	74	0
8	**14**	A	Me_3SiCl	**28**	83	0

Method A: 1, THF, half hour metallation time; **Method B**: Et_2O:THF (4:1), half hour metallation time. * %ee determined by optical rotation (see text).

The use of the other electrophiles, CH_3I, acetone, Me_2S and PhCHO (**Table 2**, entries 3-6), failed to yield better results than Me_3SiCl. The electrophiles Me_2S and acetone gave peculiar results, (**Table 2**, entries 4,5), in that they failed to incorporate at all, unlike the respectable amounts of incorporation which they gave in the case of menthyllithium (**Table 1**, entries 5 and 8).

Failure of ether as a cosolvent to produce higher levels of asymmetric induction (**Table 2**, entry 2), as was the case with menthyllithium (**5**) (**Table 1**, entry 2), was peculiar. When menthyllithium (**5**), was employed as the base, the highest ee values were obtained when the solvent was primarily ether, while for 8-phenylmenthyllithium (**6**), pure THF gave the highest ee values. The most probable reason is the way in which the base

aggregates around the complex during deprotonation. It is impossible at this point to understand exactly what type of environment is necessary for metallation to occur and what form the resulting aggregation of the remaining base molecules with the newly lithiated complex takes. Suffice to say that each base aggregates in its own way and as a result will react to changes of solvent in a manner characteristic of itself.

Over the duration of performing these experiments, it was found that the enantiomeric excess of any given reaction product, in particular **22**, was independent of the amount of starting substrate recovered. For example, the first time **12** was metallated by **6** and trapped with Me_3SiCl, the yield of **22** was only 30%, with the rest of the product mass consisting almost entirely of recovered **12**, but the ee of **16** was still very high (77%). This behaviour indicates that the equilibrium between the lithiated complex and neutral complex is slow in being established relative to incorporation of Me_3SiCl.

Overall, this methodology has some distinct practical impediments, mainly stemming from its inability to deliver consistent quantities of the chiral alkyllithium base. It was impossible on any given trial to quantify the amount of base, and as a result many reactions gave products in poor yield. The limiting factor appears to be the amount of LiDBB which can be generated before the chloride is added. Furthermore, attempts to follow Freeman's procedure,[22] in which a stoichiometric amount of lithium is cut and stirred with DBB until it dissappears, was found to be impossible. In these cases the piece of lithium was very tiny and could not be cut to expose a fresh surface, so consequently no radical anion formation was observed at all. Finally, even when a large piece of lithium was cut with a knife under a stream of argon in the mouth of the flask, LiDBB was not

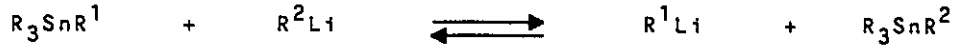
produced until scratching with needles in solution occured. The consequences of this are quite significant with respect to the lithiations of the complexes, because the exact amount of base which gave the best results are not known. To obtain this information, one would require the titration of an aliquot of the base before the complex was added, but due to the small scale (0.3 mmol) of this chemistry, titration either failed or gave unreliable results.

Aside from the inherent problem with the technical aspects of this chemistry, the main purpose of this investigation was fulfilled. Chiral alkyllithium bases could be prepared in enantiomerically pure form and metallation of (arene)tricarbonylchromium complexes could be accomplished with a high degree of asymmetric induction and in a respectable yield (77%, 80% ee).

Future Work

With an improved method for preparing the chiral alkyllithium base, many different experiments for increasing the level of asymmetric induction could be performed, such as employing different solvents like ether, or altering the number of equivalents of base. Also, the reason for lack of any asymmetric induction for the complexes **13** and **14** with the use of **6** (**Table 2**, entries 7, 8), could be further investigated in a much more facile manner.

The most promising approach, which could allow easier preparation of the chiral alkyllithium base, would be the use of the corresponding tin compound, which can equilibrate with a common alkyllithium base as indicated in **Scheme 17**.



Scheme 17

The driving force of this equilibrium is the relative difference in base strengths of the organolithium species.[29] This equilibrium, even when the relative basicities involved are close, can be heavily dependent on the reaction conditions like solvent and choice of R groups on any of the species. Thus, for this research, a tin compound corresponding to 8-phenylmenthol could be prepared via the tosylate,[30] with subsequent lithiation through the use of an appropriate commercially available alkyllithium base (**Figure 9**).

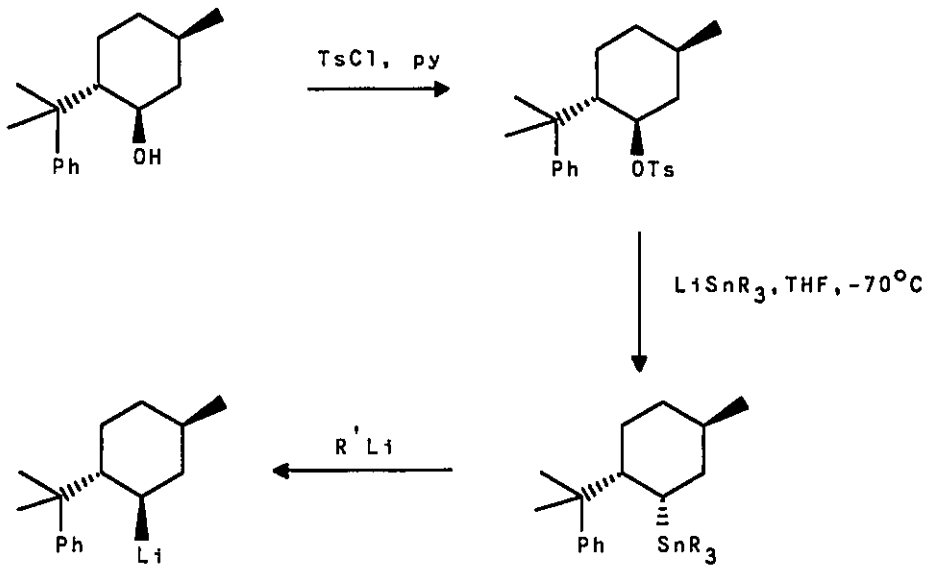


Figure 9: Alternative pathway to 8-phenylmenthyllithium

Experimental

General Methods

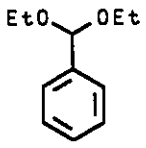
All solvents were utilized after drying over the appropriate drying agent. Diethyl ether and tetrahydrofuran were distilled from benzophenone-ketyl immediately prior to use. Butyl ether was distilled from calcium hydride.

A typical workup refers to extraction of the organic product from the aqueous phase with diethyl ether three times. The combined ether layers were then washed with brine, dried over magnesium sulphate and filtered. Evaporation of the solvent under reduced pressure afforded the crude product.

All column chromatography was performed using Merck Kieselgel 230-400 mesh silica gel, while all preparatory TLC was done using Uni-plate® 1000 micron silica gel GF plates. Analytical thin layer chromatography was performed using Merck precoated silica gel 60 F_{254} aluminium sheets. Flash chromatography followed the protocol described by Still.[31]

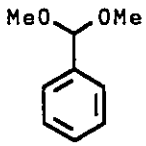
Elemental analyses were performed by M-H-W Laboratories, Phoenix, Arizona. Infrared spectra were run on a Nicolet 5DX Spectrometer or a Bomem Michelson 100. NMR spectra, given in ppm and coupling constants in hertz, were run on a Bruker AC 300 Spectrometer at 300 MHz for ^{1}H and 75 MHz for ^{13}C in $CDCl_3$ solution at 25 °C. Mass spectra were run on a Varian Kratos Profile instrument in electron impact mode. Gas chromatographic analyses were performed on a Shimadzu GC-9A instrument using a fused silica glass capillary column and a Shimadzu C-R6A recorder.

Melting points were obtained uncorrected from a Thomas Hoover, Uni-Melt® capillary melting point apparatus. Boiling points refer to bulb to bulb distillation.



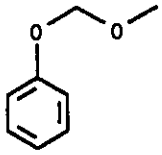
(Diethoxymethyl)benzene (10)

A solution of benzaldehyde (10.0 g) and p-toluenesulphonic acid (0.8962 g) in anhydrous ethanol was refluxed overnight. The mixture was cooled, filtered and the solvent removed under reduced pressure. Distillation yielded 14.591 g (86%) of a colourless liquid, bp 50-53 °C/0.5 torr, (Lit. 89 °C/7 torr).[32]



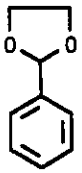
(Dimethoxymethyl)benzene (8)

The procedure for the preparation of **10** was repeated, using methanol in place of ethanol and again utilizing benzaldehyde (10.00 g). Distillation yielded 10.73 g (75%) of a colourless liquid, bp 90-91 °C/17 torr, (Lit. 87-89 °C/18 torr).[33]



(Methoxymethoxy)benzene (9)

A solution of phenol (5.0 g) and adogen (0.5 mL) were stirred in a solution of dichloromethane (200 mL) and 50% aqueous NaOH (8.5 mL) for 1 h. Chloromethyl methyl ether (6.1 mL) was then added and the solution stirred overnight. Workup followed by distillation yielded 7.02 g (95%) of a colourless liquid, bp 84-86 °C/0.9 torr, (Lit. 63-65 °C/8 torr).[34]



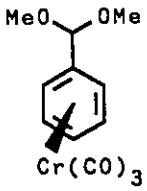
2-Phenyl-1,3-dioxolane (11)

A mixture of benzaldehyde (15 mL) and 1,2-ethanediol (8.3 mL) in benzene (150 mL), containing a catalytic quantity of p-TsOH•H_2O (0.25 g), was heated at reflux, with a Dean-Stark trap, overnight. Evaporation of the solvent followed by distillation yielded a colourless liquid, 83% bp 60-62 °C/1.0 torr, (Lit. 61-62 °C/1.0 torr).[32]

Preparation of (η^6-Arene)tricarbonylchromium(0) Complexes

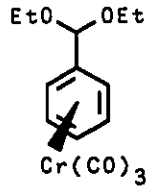
General Procedure

A mixture of arene and chromium hexacarbonyl (1 equiv) in dibutyl ether:THF (10:1) was stirred at reflux under nitrogen for 48 h, filtered through Celite® and the solvent evaporated. Chromatography using petroleum ether:EtOAc (5:1) afforded the (arene)tricarbonylchromium complex.



[η^6-(Dimethoxymethyl)benzene]tricarbonylchromium (0) (12)

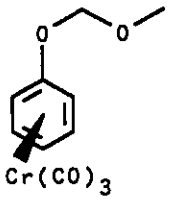
Yellow crystals were obtained in 73% yield, and were spectroscopically identical to the literature,[35] mp 37-39 °C (hexane/ether).



[η^6-(Diethoxymethyl)benzene]tricarbonylchromium (0) (14)

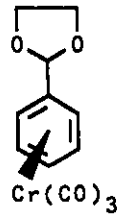
Yellow crystals were obtained in 85% yield, mp 54-55 °C (pentane/CH_2Cl_2); IR (KBr pellet) 1960, 1874 cm^{-1}; ^1H NMR, δ, 5.56 (d, 2H, J=6.3), 5.28 (m, 3H), 5.17 (s, 1H), 3.63 (m,

4H), 1.22 (t, 6H, J=7.1); ^{13}C NMR, δ, 232.7, 108.4, 99.8, 92.6, 91.9, 91.7, 62.2, 15.2; MS m/e 316 (M+); Anal. Calcd. for $C_{14}H_{16}O_5Cr$; C, 53.16; H, 5.06. Found: C, 53.19; H, 5.29.



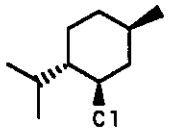
[η⁶-(Methoxymethoxy)benzene]tricarbonylchromium (0) (13)

Yellow crystals were obtained in 74% yield, mp 77-78 °C (pentane/ether); IR (KBr pellet) 1950, 1861 cm^{-1}; ^1H NMR, δ, 5.53 (t, 2H, J=6.5Hz), 5.30 (d, 2H, J=6.5Hz), 5.07 (s, 2H), 4.91 (t, 1H, J=6.1Hz), 3.50 (s, 3H); ^{13}C, δ, NMR 233.1, 140.6, 95.2, 94.6, 86.0, 80.5, 56.9; MS m/e 274 (M^+); Anal. Calcd. for $C_{11}H_{10}CrO_5$; C, 48.18; H, 3.65. Found: C, 48.39; H, 3.63.



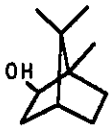
[η⁶-2-Phenyl-1,3-dioxane]tricarbonylchromium (0) (15

Yellow crystals were obtained in 80% yield, mp 106-107 °C (pentane/ether), (Lit. 107-108 °C).[9]



(-) Menthyl Chloride (17)

Prepared **17** in 90% yield according to the method used by Smith and Wright[24] except that the mixture was stirred at room temperature for 3 days. Distillation gave a colourless liquid, bp 109-112 °C/25 torr; (Lit. 101-101.5 °C/21 torr)[24]; [α] -49.16° (c 2.98, ethanol), (Lit. [α] -45.0°).[24]

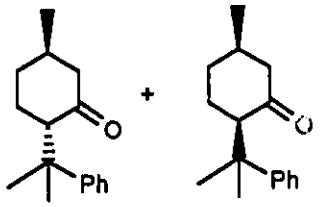


(-)-Isoborneol (19)

$LiAlH_4$ (1.5 g) was placed in a round-bottomed flask (500 mL) with THF (200 mL). (+)-Camphor (4.0 g) was then added as a solution in THF (10 mL) to the $LiAlH_4$ suspension over a period of 10 min. The resulting mixture was refluxed overnight and water subsequently added carefully. The product was extracted with ether in the typical manner. Removal of the solvent yielded **19** (3.81 g, 94%), mp 205-207 °C (petroleum ether/ethanol), (Lit. 213 °C)[25]; [α] -19.82° (c 1.12, ethanol), [Lit. [α] -34.3° (ethanol)].[36]

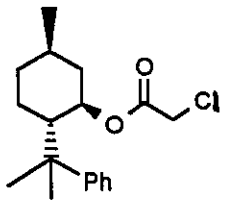
2-Bornyl Chloride (20)

Into a round-bottomed flask (250 mL) was placed (-)-isoborneol (9.5 g), 37% HCl (200 mL) and $ZnCl_2$ (24 g). This mixture was stirred for three days at room temperature. The product was extracted with ether in the usual way and the solvent removed to yield **20** (8.91 g, 84%), mp 131-132 °C (ethanol), (Lit. 131-132 °C)[26]; [α] -1.63° (c 0.8, Et_2O), [Lit. [α] -34.5° (c 2.0, Et_2O)].[26]



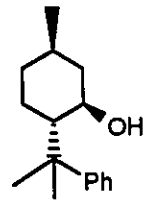
(2R, 5R)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexanone and (2S, 5R)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexanone

An oil was obtained in 83% yield when following the procedure of Oswald,[27] bp 110-115 °C/0.2 torr, (Lit. 100-110 °C/0.05 torr).[27]



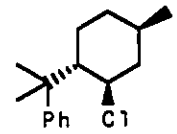
(1R, 2S, 5R)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl chloroacetate

A white solid was obtained in 51% yield when following the procedure of Oswald,[27] mp 83 °C, (Lit. 82-83 °C).[27]



(1R, 2S, 5R)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexanol or 8-Phenylmenthol

A colourless oil was obtained in 88% yield when following the procedure of Oswald,[27] bp 115-123 °C/0.15 torr, (Lit. 105-115 °C/ 0.01 torr);[27] [α] -26.0° (c 1.51, ethanol), (Lit. [α] -26.4° (c 1.97, ethanol)).[27]



(1R, 2S, 5R)-1-Chloro-5-methyl-2-(1-methyl-1-phenylethyl)cyclohexane (21)

Thionyl chloride (50 mL) was poured over ice-cooled 8-phenylmenthol (12.45 g) in a round-bottomed flask (250 mL). The mixture was stirred for 1 h, removed from the ice bath, and stirred at room temperature overnight. Water was added slowly to consume the excess

thionyl chloride, the the mixture subjected to the conventional workup. Distillation of the crude oil yielded **21** (11.0 g, 82%), bp 112-115 °C/0.22 torr; [α] -40.12° (c 0.67, CH_2Cl_2); IR (neat, NaCl) 3087, 2951, 1599, 765, 699 cm^{-1}; [α] -40.12° (c 0.67, CH_2Cl_2); ^1H NMR, δ, 7.2-7.4 (m, 5H), 3.85 (m, 1H), 1.51 (s, 3H), 1.34 (s, 3H), 0.87 (d, 3H, J=5.9Hz), 0.85-2.2 (m, 8H); ^{13}C NMR, δ, 151.3, 127.9, 125.9, 125.4, 62.7, 53.8, 48.5, 41.2, 34.6, 33.4, 28.9, 28.0, 26.4, 21.8; MS m/e 250 (M^+); Anal. Calcd. for $C_{16}H_{23}Cl$: C, 76.62; H, 9.24. Found C, 76.74: H, 9.40.

Procedures for the preparation of enantiomerically enriched complexes using a chiral base

Method A:

DBB (0.2 g) was placed in a round-bottomed flask (100 mL) under argon with THF (10 mL) and a glass stirring bar. A dime size chunk of freshly cut lithium was then added quickly and cut and scratched in the solution with two syringe needles. The solution was cooled to -78 °C and stirred for 4-5 h, at which point 8-phenylmenthyl chloride (0.15 mL) was added and the solution stirred for 2 min. The (arene)tricarbonylchromium (0) complex of choice (50-100 mg) was added in THF (1 mL) and the solution stirred for 0.5 h. The electrophile of choice (1.5 equivalents with respect to the complex) was added, and the solution stirred for an additional hour and quenched with water. A typical workup yielded the crude product.

Method B:

DBB (0.2 g) was placed in a round-bottomed flask (100 mL) under argon with THF (3 mL) and a glass stirring bar. A dime size chunk of freshly cut lithium was then added quickly and cut and scratched in the solution with two syringe needles. The solution was cooled to -78 °C and stirred for 4-5 h at which point 8-phenylmenthyl chloride (0.15 mL) was added and the solution stirred for 2 min. Et_2O (10 mL) is then added to the solution and allowed to stir for 2-3 min. The (arene)tricarbonylchromium (0) complex of choice (50-100 mg) was added in Et_2O (2 mL) and the solution stirred for 0.5 h. The electrophile of choice (1.5 equivalents with respect to the complex) was added, and the solution stirred for an additional hour and quenched with water. A typical workup yielded the crude product.

Method C:

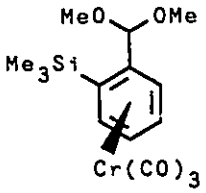
DBB (0.2 g) was placed in a round-bottomed flask (100 mL) under argon with THF (10 mL) and a glass stirring bar. A dime size chunk of freshly cut lithium was then added quickly and cut and scratched in the solution with two syringe needles. The solution was cooled to -78 °C and stirred for 4-5 h, at which point menthyl chloride (0.15 mL) was added and the solution stirred for 2 min. The (arene)tricarbonylchromium (0) complex of choice (50-100 mg) was added in THF (1 mL) and the solution stirred for 0.5 h. The electrophile of choice (1.5 equivalents with respect to the complex) was added, and the solution stirred for an additional hour and quenched with water. A typical workup yielded the crude product.

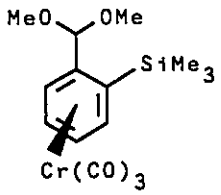
Method D:

DBB (0.2 g) was placed in a round-bottomed flask (100 mL) under argon with THF (3 mL) and a glass stirring bar. A dime size chunk of freshly cut lithium was then added quickly and cut and scratched in the solution with two syringe needles. The solution was cooled to -78 °C and stirred for 4-5 h, at which point menthyl chloride (0.15 mL) was added and the solution stirred for 2 min. Et_2O (10 mL) was then added to the solution and allowed to stir for 2-3 min. The (arene)tricarbonylchromium (0) complex of choice (50-100 mg) was added in Et_2O (2 mL) and the solution stirred for 0.5 h. The electrophile of choice (1.5 equivalents with respect to the complex) was added, and the solution stirred for an additional hour and quenched with water. A typical workup yielded the crude product.

Method E:

DBB (0.2 g) was placed in a round-bottomed flask (100 mL) under argon with THF (10 mL) and a glass stirring bar. A dime size chunk of freshly cut lithium was then added quickly and cut and scratched in the solution with two syringe needles. The solution was cooled to -78 °C and stirred for 4-5 h, at which point menthyl chloride (0.15 mL) was added and the solution stirred for 2 min. The (arene)tricarbonylchromium (0) complex of choice (50-100 mg) was added in THF (1 mL) and the solution stirred for 10 min. The electrophile of choice (1.5 equivalents with respect to the complex) was added, and the solution stirred for an additional hour and quenched with water. A typical workup yielded the crude product.





(1R, 2R)-[η⁶-1-(Dimethoxymethyl)-2-trimethylsilylbenzene]tricarbonylchromium(0) and (1S, 2S)-[η⁶-1(Dimethoxymethyl)-2-trimethylsilylbenzene]tricarbonylchromium(0) (22)

Compound **12** (92 mg), was lithiated according to Method A, using Me_3SiCl as the electrophile. Purification of the crude product through column chromatography (10:1 petroleum ether:Et_2O) afforded **(1R, 2R)-22** (88 mg, 77%), mp 85-88 °C (petroleum ether/ether); [α] +41.85° (c 0.26, CH_2Cl_2). Compound **(1R, 2R)-22** was spectroscopically identical to the literature compound.[35] ^1H NMR spectroscopy in conjunction with $Eu(hfc)_3$ indicated an 80% ee (1R, 2R), by integration of the CH_3O resonances of the two enantiomers.

Compound **12** (75 mg), was lithiated according to Method B, using Me_3SiCl as the electrophile. Purification of the crude product through column chromatography (10:1 petroleum ether:Et_2O) afforded **(1R, 2R)-22** (69 mg, 77%), [α] +25.6° (c 0.5, CH_2Cl_2). ^1H NMR spectroscopy in conjunction with $Eu(hfc)_3$ indicated an 54% ee (1R, 2R), by integration of the CH_3O resonances of the two enantiomers.

Compound **12** (93 mg), was lithiated according to Method C, using Me_3SiCl as the electrophile. Purification of the crude product through column chromatography (10:1 petroleum ether:Et_2O) afforded **(1S, 2S)-22** (86 mg, 85%), [α] -10.11° (c 0.12, CH_2Cl_2). ^1H

NMR spectroscopy in conjunction with $Eu(hfc)_3$ indicated an 35% ee (1S, 2S), by integration of the CH_3O resonances of the two enantiomers.

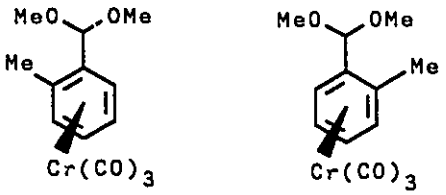
Compound **12** (100 mg), was lithiated according to Method D, using Me_3SiCl as the electrophile. Purification of the crude product through column chromatography (10:1 petroleum ether:Et_2O) afforded **(1S, 2S)-22** (71 mg, 57), $[\alpha]$ -22.22° (c 0.11, CH_2Cl_2). ^1H NMR spectroscopy in conjunction with $Eu(hfc)_3$ indicated an 70% ee (1S, 2S), by integration of the CH_3O resonances of the two enantiomers.

Compound **12** (41 mg), was lithiated according to Method E, using Me_3SiCl as the electrophile. Purification of the crude product through column chromatography (10:1 petroleum ether:Et_2O) afforded **(1S, 2S)-22** (20 mg, 38%), $[\alpha]$ -10.1° (c1.0, CH_2Cl_2). ^1H NMR spectroscopy in conjunction with $Eu(hfc)_3$ indicated an 32% ee (1S, 2S), by integration of the CH_3O resonances of the two enantiomers.

Sample procedure for using the chiral lanthanide shift reagent $Eu(hfc)_3$

A sample of **22** (4-5 mg) was dissolved in chloroform-d (1.5-2.0 mL) and placed in an NMR tube. $Eu(hfc)_3$ (15 mg) was dissolved in chloroform-d (2.0 mL) and placed in a vial. After obtaining a proton spectrum, half of the shift reagent solution was added to the NMR tube by pipette, and the proton spectra run again. If the enantiomer peaks are not separated enough, then small aliquots of the remaing shift reagent solution can be added each time

running a proton spectra, and observing the enantiomer resonances separation. A spectra of 22 showing 80% ee is included at the end of this experimental section.



(1S, 2R)-[η⁶-1-(Dimethoxymethyl)-2-methylbenzene]tricarbonylchromium (0) and (1R, 2S)-[η⁶-1-(Dimethoxymethyl)-2-methylbenzene]tricarbonylchromium (0) (23)

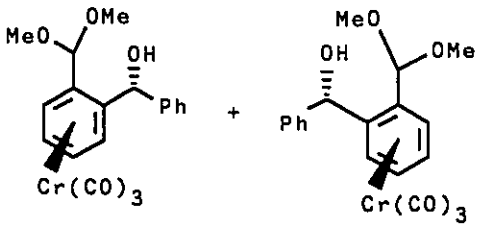
Compound 12 (50 mg), was lithiated according to Method A, using CH_3I as the electrophile. Purification of the crude product through column chromatography (5:1 petroleum ether:EtOAC) afforded **(1S, 2R)-23** (11 mg, 21%, 90% by recovered substrate), yellow crystals mp 64-65 °C (pentane); [α] -30.0° (c 0.08, CH_2Cl_2); IR (KBr pellet) 1957, 1888, 1858 cm^{-1}; ^1H NMR, δ, 5.82 (m, 1H), 5.36 (m, 1H), 5.18 (s, 1H), 5.17 (m, 1H), 5.10 (d,1H, J=6.1), 3.56 (s, 3H), 3.23 (s, 3H), 2.20 (s, 3H); ^{13}C NMR, δ, 233.0, 108.2, 105.0, 100.4, 94.2, 93.6, 92.7, 89.3, 57.0, 51.2, 18.5; MS m/e 302 (M^+); Anal. Calcd. for $C_{13}H_{14}CrO_5$: C, 51.66; H, 4.64. Found: C, 51.79; H, 4.69. The enantiomeric excess was measured by comparision of the optical rotation with that of the product obtained from method C, indicating an ee of 73.5% (1S, 2R).

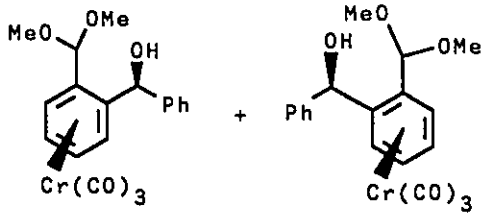
Compound 12 (85 mg), was lithiated according to Method C, using $(MeO)_2SO$ as the electrophile. Purification of the crude product through column chromatography (5:1

petroleum ether:EtOAC) afforded **(1R, 2S)-23** (22 mg, 25%, 85% by recovered substrate), [α] +11.67° (c 0.21, CH_2Cl_2). ^1H NMR spectroscopy in conjunction with $Eu(hfc)_3$ indicated an 30% ee (1R, 2S), by integration of the CH_3O resonances of the two enantiomers.

Compound **12** (98 mg), was lithiated according to Method C, using CH_3I as the electrophile. Purification of the crude product through column chromatography (5:1 petroleum ether:EtOAc) afforded **(1R, 2S)-23** (10 mg, 10%, 68% by recovered substrate), [α] +5.71° (c 0.28, CH_2Cl_2). ^1H NMR spectroscopy in conjunction with $Eu(hfc)_3$ indicated an 15% ee (1R, 2S),by integration of the CH_3O resonances of the two enantiomers.

Compound **12** (100 mg), was lithiated according to Method D, using CH_3I as the electrophile. Purification of the crude product through column chromatography (5:1 petroleum ether:EtOAC) afforded **(1R, 2S)-23** (64 mg, 61%, 76% by recovered substrate), [α] +20.39° (c 0.28, CH_2Cl_2). ^1H NMR spectroscopy in conjunction with $Eu(hfc)_3$ indicated an 56% ee (1R, 2S), by integration of the CH_3O resonances of the two enantiomers.





(1R, 2S, 2'R) and (1S, 2R, 2'S); (1R, 2S, 2'S) and (1S, 2R, 2'R) - [η^6-1-(Dimethoxymethyl)-2-(hydroxyphenylmethyl)benzene]tricarbonylchromium(0) (24)

At this time it is not known which diastereomer corresponds to either one of the two sets of characterization data. Consequently, the one which runs off the column first was labelled diastereomer #1 for this experimental.

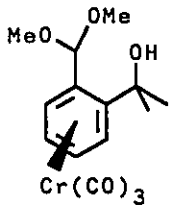
Compound **12** (105 mg), was lithiated according to Method A, using PhCHO as the electrophile. Purification of the crude product through column chromatography (5:1 petroleum ether:EtOAC) afforded diastereomer #1 (43%) and diastereomer #2 (30%).

Diastereomer #1: Yellow oil, [α] +120.8 (c 0.12, CH_2Cl_2); IR (NaCl neat) 3439, 1961, 1876 cm^{-1}; ^1H NMR 7.33 (m, 5H), 5.76 (d, 1H, J=3.3), 5.70 (m, 2H), 5.38 (s, 1H), 5.37 (m, 2H), 3.52 (s, 3H), 2.87 (s, 3H), 2.44 (d, 1H, J=3.3); ^{13}C NMR 232.6, 141.5, 128.6, 128.3, 127.4, 114.4, 106.2, 99.8, 92.2, 91.8, 91.3, 90.6, 70.3, 56.6, 50.8; MS m/e 394 (M+); HRMS m/e for $C_{19}H_{18}O_6Cr$ calcd. (M+) 394.0508, found 394.0504. ^1H NMR spectroscopy in

conjunction with $Eu(hfc)_3$ indicated an 60% ee (1S, 2R), by integration of the CH_3O resonances of the two enantiomers.

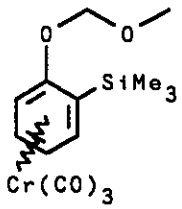
Diastereomer #2: Yellow oil, [α] +63.3° (c 0.3, CH_2Cl_2); IR (NaCl neat) 3443, 1966, 1882 cm^{-1}; ^1H NMR 7.56 (d, 1H, J=7.7), 7.37 (m, 4H), 5.83 (d, 1H, J=2.1), 5.70 (s, 1H), 5.58 (d, 1H, J=6.9), 5.41 (t, 1H, J=6.7), 5.10 (t, 1H, J=6.9), 4.69 (d, 1H, 6.3), 4.47 (d, 1H, J=2.3), 3.65 (s, 3H), 3.38 (s, 3H); ^{13}C NMR (In C_6D_6) 232.4, 138.6, 128.6, 127.9, 127.2, 112.1, 106.1, 100.2, 93.6, 92.7, 90.9, 88.8, 70.6, 56.6, 50.5; MS m/e 394 (M+); HRMS m/e for $C_{19}H_{18}O_6Cr$ calcd. (M+) 394.0508, found 394.0503. ^1H NMR spectroscopy in conjunction with $Eu(hfc)_3$ failed to give an interpretable spectrum.

Compound **12** (100 mg), was lithiated according to Method C, using PhCHO as the electrophile. Purification of the crude product through column chromatography (5:1 petroleum ether:EtOAc) afforded diastereomer #1 (35 mg, 26%), [α] -58.1° (c 0.14, CH_2Cl_2); ^1H NMR spectroscopy in conjunction with $Eu(hfc)_3$ indicated an 32% ee (1R, 2S), by integration of the CH_3O resonances of the two enantiomers; and diastereomer #2 (32 mg, 24%), [α] -30.5° (c 0.21, CH_2Cl_2); ^1H NMR spectroscopy in conjunction with $Eu(hfc)_3$ failed to give an interpretable spectrum.



(1R,2S)-[η⁶-1-(Dimethoxymethyl)-2-(hydroxy-1-methylethyl)benzene]tricarbonylchromium(0) (25)

Compound **12** (78 mg), was lithiated according to Method C, using acetone as the electrophile. Purification of the crude product through column chromatography (5:1 petroleum ether:EtOAC) afforded **25** (66 mg, 71%), mp 82-83°C (pentane/ether); [α] +4.57° (c 0.38, CH_2Cl_2); IR (KBr pellet) 3450, 1964, 1881 cm^{-1}; ^1H NMR, δ, 6.04 (s, 1H), 5.79 (d, 1H, J=6.5), 5.40 (m, 1H), 5.28 (m, 2H), 3.57 (s, 3H), 3.32 (s, 3H), 2.69 (s, 1H, exchangeable), 1.64 (s, 3H), 1.59 (s, 3H); ^{13}C NMR, δ, 231.2, 117.1, 104.5, 98.6, 90.4, 90.3, 89.9, 89.3, 71.6, 55.8, 50.1, 31.1, 29.8; MS m/e 346 (M^+); Anal. Calcd. for $C_{15}H_{18}CrO_6$: C, 52.02; H, 5.20. Found: C, 52.06; H, 5.11. ^1H NMR spectroscopy in conjunction with Eu(hfc)$_3$ did not give an interpretable spectrum.

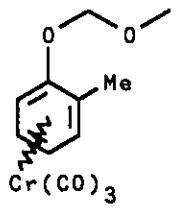


[η⁶-1-(methoxymethoxy)-2-trimethylsilylbenzene]tricarbonylchromium (0) (26)

Compound **13** (92 mg), was lithiated according to Method A, using Me_3SiCl as the electrophile. Purification of the crude product through column chromatography (10:1

petroleum ether:Et_2O) afforded **26** (99 mg, 85%), mp 70-72 °C (pentane); [α] 0° (c 1.5, CH_2Cl_2); IR (KBr pellet) 1951, 1862 cm^{-1}; ^1H NMR, δ, 5.83 (m, 1H), 5.55 (m, 1H), 5.26 (d, 1H, J=7.0), 5.15 (d, 1H, J=7.2), 4.97 (d, 1H, J=7.2), 4.78 (d, 1H, J=6.0), 3.46 (s, 3H), 0.31 (s, 9H); ^{13}C NMR, δ, 233.7, 145.1, 101.4, 96.1, 94.7, 88.9, 85.4, 76.7, 57.0, -0.5; MS m/e 346 (M^+); Anal. Calcd. for $C_{14}H_{18}CrO_5Si$: C, 48.55; H, 5.20. Found: C, 48.57; H, 5.12. ^1H NMR spectroscopy in conjunction with $Eu(hfc)_3$ indicated 0% ee by integration of the CH_3O resonances.

Compound **13** (50 mg), was lithiated according to Method C, using Me_3SiCl as the electrophile. Purification of the crude product through column chromatography (10:1 petroleum ether:Et_2O) afforded **26** (51 mg, 81%), mp 70-72 °C (pentane); [α] +7.78° (c 0.18, CH_2Cl_2). ^1H NMR spectroscopy in conjunction with $Eu(hfc)_3$ indicated an 32% ee (which enantiomer is in excess is not known) by integration of the CH_3O resonances of the two enantiomers.

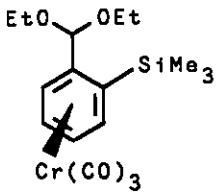


[η^6-1-(Methoxymethoxy)-2-methylbenzene]tricarbonylchromium (0) (27)

Compound **13** (150 mg), was lithiated according to Method C, using CH_3I as the electrophile. Purification of the crude product through column chromatography (5:1

petroleum ether:EtOAC) afforded 27 (20 mg, 13%, 75% by recovered substrate), oil, [α] +7.2° (c 0.08, CH_2Cl_2); IR (NaCl neat) 1965, 1867 cm^{-1}; ^1H NMR, δ, 5.44 (overlapping apparent doublets, 2H), 5.30 (apparent t, 1H, J=6.8), 5.12 (d, 1H, J=7.0), 5.02 (d, 1H, J=7.0), 4.95 (apparent t, 1H, J=6.4), 3.49 (s, 3H), 2.15 (s, 3H); ^{13}C NMR, δ, 233.7, 138.7, 99.1, 96.2, 95.8, 92.4, 87.7, 80.0, 56.9, 16.3; MS m/e 288 (M+); HRMS m/e for $C_{12}H_{12}O_5Cr$ calcd. (M+) 288.00897, found 288.01855. ^1H NMR spectroscopy in conjunction with $Eu(hfc)_3$ indicated an 15% ee (which enantiomer is in excess is not known), by integration of the CH_3O resonances of the two enantiomers.

Compound 13 (80 mg), was lithiated according to Method D, using CH_3I as the electrophile. Purification of the crude product through column chromatography (5:1 petroleum ether:EtOAC) afforded 27 (8 mg, 10%, 91% by recovered substrate), [α] +17.8° (c 0.17, CH_2Cl_2). ^1H NMR spectroscopy in conjunction with $Eu(hfc)_3$ indicated an 40% ee (which enantiomer is not known), by integration of the CH_3O resonances of the two enantiomers.

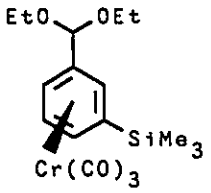


(1R, 2S)-[η ^{6}-1-(Diethoxymethyl)-2-trimethylsilylbenzene]tricarbonylchromium (0) (28)

Compound 14 (51 mg), was lithiated according to Method A, using Me_3SiCl as the electrophile. Purification of the crude product through column chromatography (10:1

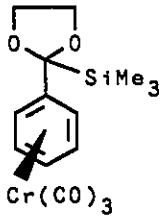
petroleum ether:Et_2O) afforded **28** (46 mg, 74%) as yellow crystals, mp 57-59 °C (pentane); [α] 0° (c 0.9, CH_2Cl_2); IR (KBr pellet) 1959, 1874 cm^{-1}; ^1H NMR, δ, 5.64 (d, 1H, J=6.5), 5.56 (t, 1H, J=6.3), 5.39 (d, 1H, J=7.0), 5.37 (s, 1H), 5.16 (t, 1H, J=6.1), 3.34-3.80 (four multiplets, 4H), 1.27 (t, 3H, J=7.1), 1.15 (t, 3H, J= 7.1), 0.35 (s, 9H); ^{13}C NMR, δ, 233.2, 114.3, 100.1, 98.5, 94.3, 91.1, 89.8, 89.7, 64.8, 58.0, 15.2, 15.1, 0.6; MS m/e 388 (M^+); Anal. Calcd. for $C_{17}H_{24}CrO_5Si$: C, 52.58; H, 6.19. Found: C, 52.42; H, 6.14. ^1H NMR spectroscopy in conjunction with $Eu(hfc)_3$ of the corresponding aldehyde (**29**), indicated a 0% ee by integration of the CHO resonances of the two enantiomers;

Compound **14** (80 mg), was lithiated according to Method C, using Me_3SiCl as the electrophile. Purification of the crude product through column chromatography (10:1 petroleum ether:Et_2O) afforded **28** (69 mg, 71%, 83% by recovered substrate). ^1H NMR spectroscopy in conjunction with $Eu(hfc)_3$ of the corresponding aldehyde (**29**), indicated an 30% ee (1R, 2S), by integration of the CHO resonances of the two enantiomers. A trace amount (<4 mg) of the meta isomer was obtained under these conditions and is characterized next.



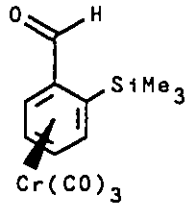
[η⁶-1-(Diethoxymethyl)-3-trimethylsilybenzene]tricarbonylchromium (0)

This was obtained in trace amounts (4 mg) from the application of Method C on **14**; viscous yellow oil; IR (neat, NaCl) 1966, 1888 cm^{-1}; ^1H NMR, δ, 5.75 (d, 1H, J=6.5), 5.64 (s, 1H), 5.39 (d, 1H, J=6.1), 5.16 (t, 1H, J=6.3), 5.09 (s, 1H), 3.64 (m, 4H), 1.24 (m, 6H), 0.28 (s, 9H); ^{13}C NMR, δ, 232.9, 106.0, 100.3, 99.5, 98.5, 98.1, 94.3, 89.6, 62.9, 62.5, 15.2,-1.1; MS m/e 388 (M^+); Anal. Calcd. for $C_{17}H_{24}CrO_5Si$: C, 52.58; H, 6.19. Found: C, 52.39; H, 6.29.



[η⁶-2-Phenyl-2-trimethylsilyl-1,3-dioxolane]tricarbonylchromium (0) (30)

Compound **15** (100 mg), was lithiated according to Method C, using Me_3SiCl as the electrophile. Purification of the crude product through column chromatography (10:1 petroleum ether:Et_2O) afforded **30** (90 mg, 72%) as yellow crystals, mp 148-151 °C (petroleum ether/ether), (Lit. mp 148-150 °C).[9]



(1S, 2S)-[η^6-2-trimethylsilylbenzaldehyde]tricarbonylchromium (0) (29)

Compound **29** was prepared by a modification of the procedure of Davies, changing the reaction time from 6 h to 2 h. The viscous orange oil was spectroscopically identical to the literature.[35]

PPM

3.5935
3.5931

3.1417

MJS-225

+ $Eu(hfc)_3$

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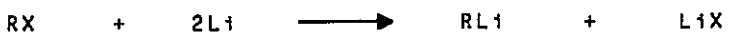
Happy the eyes that need no illusion to see that the spectacle is great! It is illusion that teaches the others to look, to admire, and rejoice. And look as high as they will, they never can look too high. Truth rises as they draw nearer; they draw nearer when they admire. And whatever the heights may be whereon they rejoice, this rejoicing can never take place in the void, or above the unknown and eternal truth that rests over all things like beauty in suspense.

- Maurice Maeterlinck, *The Life of the Bee*

Chapter 2: Reductive Lithiation of (Arene)tricarbonylchromium Acetals

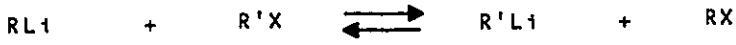
Introduction

Organolithium compounds have become an integral part of organic synthesis, and because of their usefulness and versatility there exists a multitude of methods for generating and utilizing these compounds.[1] There are four common methods for creating an organolithium, the most popular of which is the reaction of lithium metal and an organic halide (**Scheme 1**). This is the method currently employed by commercial providers of common organolithium reagents such as butyllithium or methyllithium.



Scheme 1

A second method for organolithium preparation is metal halogen exchange, whereby an organolithium reagent such as butyllithium undergoes exchange with an organic halide (**Scheme 2**). Typically, the substrate is an aryl or an allyl halide, but some recent work suggests that some primary alkyl iodides can undergo this reaction as well.[1]



Scheme 2

Metallation is the third common method for preparation of organolithiums, in which a reagent such as butyllithium abstracts a proton from a substrate, thereby lithiating that site (**Scheme 3**). This, like metal halogen exchange, is most common in aryl compounds[2] and acetylenic compounds.

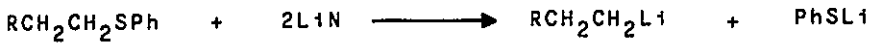
Scheme 3

The last typical method (**Scheme 4**), is the reaction of, most commonly, organic halides with radical anions. This pathway is essentially identical to the first method mentioned, the distinction being somewhat arbitrary. Aromatic systems such as naphthalene and biphenyls are typically the carriers for the electron of these radical anions. Once the reaction between the aromatic compound and the lithium is complete the resulting anion is named with the suffix 'ide". Thus naphthalene in its radical anion form if reacted with lithium would be called lithium naphthalenide. This method is both fairly recent and is increasing in popularity.

Scheme 4

In the 1970's the groundwork for the reaction of organic halides with radical anions was laid out. Since the "old fashioned" method of reacting lithium metal and an organic halide was thought to go by a radical mechanism it seemed likely that an electron carrier such as a radical

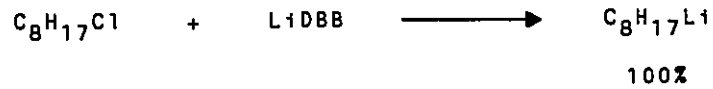
anion could facilitate the process more efficiently. Screttas showed that a thiophenyl entity could act as a functional group which could be exchanged for lithium, utilizing lithium naphthenalide (LiN), (**Scheme 5**).[3] Various alkyl thiophenyl compounds consistently gave 60-100% lithiation.



Scheme 5

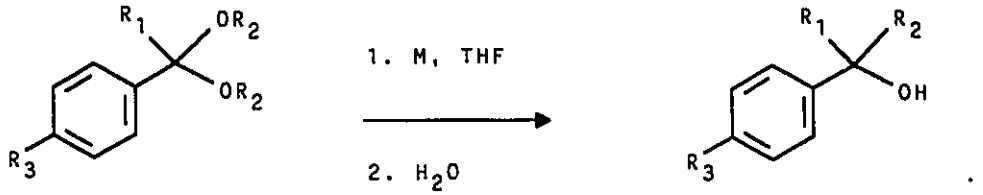
Cohen has done extensive work with organoalkali compounds which are made by reductive metalation of phenyl thioethers.[4] The radical anion which Cohen utilizes, however, is lithium 1-(dimethylamino)-naphthalenide (LDMAN).

Freeman postulated that a carbon-halide bond would be much more conducive to lithiation by this method, and that a more sterically hindered radical anion would cut down on the amount of Wurtz type coupling which could occur.[5] Freeman was able to show (**Scheme 6**), that lithium 4,4'-di(*tert*-butyl)biphenyl (LiDBB) could consistently lithiate a variety of alkyl halides in a matter of seconds in 96-100% yield. The fact that the DBB (which is not especially cheap) can easily be recovered makes this chemistry practical.



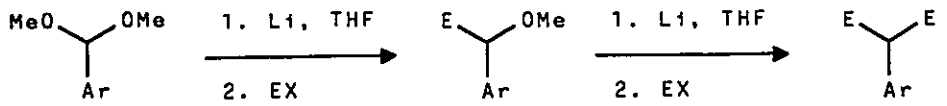
Scheme 6

Azzena further broadened the applicability of electron transfer metallations by employing lithium in the reduction of acetals and ketals.[6] A variety of aromatic acetals and ketals could be lithiated by stirring them with lithium metal at room temperature. The lithiation was followed by a Wittig type rearrangement to give the carbinol (**Scheme 7**), with yields typically in the 70-75% range.



Scheme 7

Azzena performed further investigations into reductions of acetals and ketals by radical anion induced electron transfer, and found that the Wittig rearrangement could be eliminated if low temperatures were maintained (**Scheme 8**).[7] It is worth pointing out that until this work was done, a stable α-methoxyphenylmethyl carbanion in THF had never been made without an immediate rearrangement occurring. It is thought that these carbanions might be intermolecularly stabilized by the lithium methoxide present in the reaction mixture.



52-92%

Scheme 8

There has been a fair amount of research previously done on the cleavage of ethers by sodium or potassium in liquid ammonia.[8] The bulk of this research laid the groundwork for the chemistry of Screttas, Freeman and Azzena, who essentially used the same idea of electron transfer to cleave and subsequently lithiate certain functional groups.

To demonstrate mechanistically how these cleavages are generally thought to take place, the reaction of aryl alkyl ethers with alkali metal can be used.[8] Initially, an electron transfer from the alkali metal to an aryl π^* orbital yields a radical anion (**Figure 1**). At this point, an electron transfer occurs from the π^* to either the σ^* of the (R-O) bond or the σ^* of the (Ph-O) bond, with subsequent cleavage of the corresponding bond to give the alkoxide and radical anion. After this step, there is another electron transfer from the alkali metal to the resulting radical to finally make the two anions. The transfer which occurs can be kinetically or thermodynamically controlled, and this has been found to depend on the functional group involved.[8] In the case of aryl ether functions, the transfer from the π^* to the σ^* (Ph-O) is higher in energy than the π^* to the σ^* (R-O), thus making aryl alkyl ether cleavages by alkali metals kinetically controlled. It should be pointed out, however, that changing the conditions such as solvent, or adding catalysts like naphthalene or biphenyl, has dramatic effects on the

kinetic barrier, so that in many cases either cleavage pathway can be obtained by altering the conditions.[8]

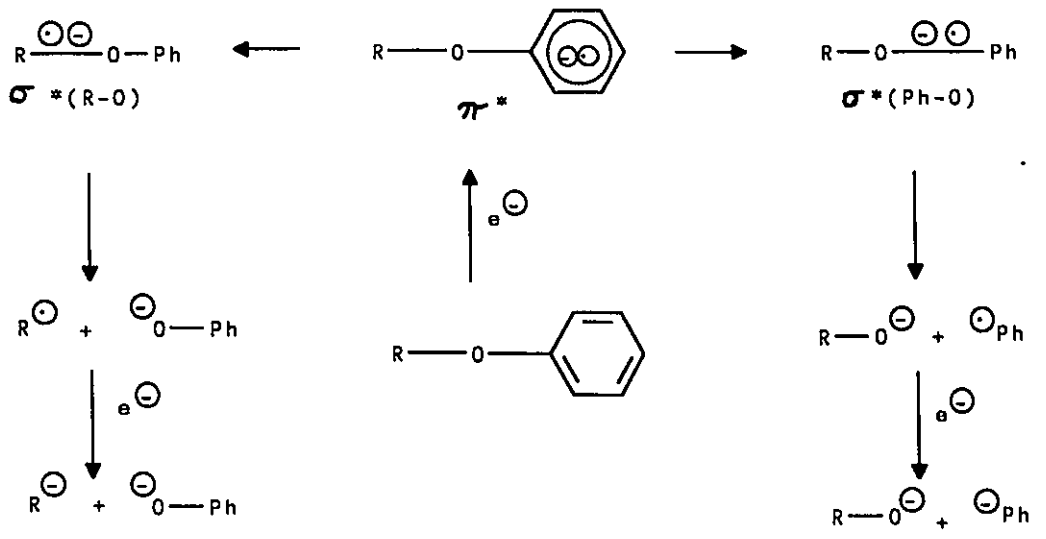
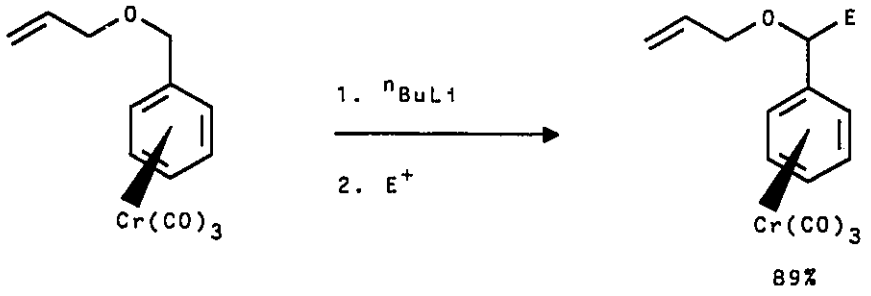


Figure 1: Pathway for aryl alkyl ethers and lithium metal

In the case of phenyl thioethers, the cleavage with few exceptions takes place between the alkyl-sulfur bond. This indicates that the π^* to σ^* (R-S) transfer occurs quite readily, unlike in the case of aryl alkyl ethers. In fact, even when there is no π^* orbital available, the electron transfer can still take place directly into the σ^*.

With this idea for the mechanism in mind, one can then rationalize how the lithiation takes place when alkyl halides are treated with LiDBB. Much like the thiophenyl group, electron transfer from LiDBB must be directly able to take place with the σ^* (R-X) of the alkyl halide. The mechanism which Azzena[6] presents follows the reasoning which has been outlined above.

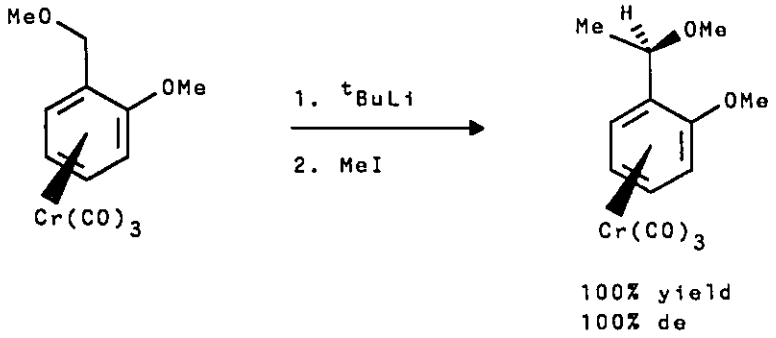
An interesting variation of LiDBB methodology would be to use it in conjunction with (arene)tricarbonylchromium complexes. The benefits of utilizing these species in organic synthesis was mentioned previously in **Chapter 1**. It can be envisioned that an aryl acetal complexed to chromium could be reduced by LiDBB to form the resulting benzylic anion. Once this benzylic anion is formed, the stablizing effect of the chromium tricarbonyl group should render the anion stable and at the same time suppress the possible Wittig rearrangement from occurring. Previous work by Davies[9] shows clearly that complexing benzyl alkyl ethers to chromium allows for deprotonation of the benzylic site and subsequent electrophilic trapping of the anion without competition from Wittig rearrangements. An example of this is shown in **Scheme 9**.



Scheme 9

Another aspect of benzylic anions of chromium arene complexes is their ability to trap electrophiles in a stereoselective fashion, when a group is present in the ortho position to the benzyl ether function.[10] Davies has demonstrated this by utilizing a methoxy substituent in the

ortho position to obtain quantitatively one stereoisomer with complete stereoselectivity. **(Scheme 10).**[11]



Scheme 10

The question which needed to be addressed was whether or not an arene chromium complex would survive radical anion formation. The reduction of (arene)tricarbonylchromium complexes by single electron donors, such as the alkali metals, is well established.[12] Rieke's group was able to show that for a variety of (arene)tricarbonylchromium complexes in which the arene had no substituents other than hydrocarbon fragments, two successive electron transfers occurred.[13] The first transfer gave a 19e$^-$ system which, being unstable, altered its coordination by forming a 17e$^-$ η^4-complex (this complex was proposed and is as yet unproven). Another electron transfer then restores the 18e$^-$ system, which is still η^4 **(Figure 2).**

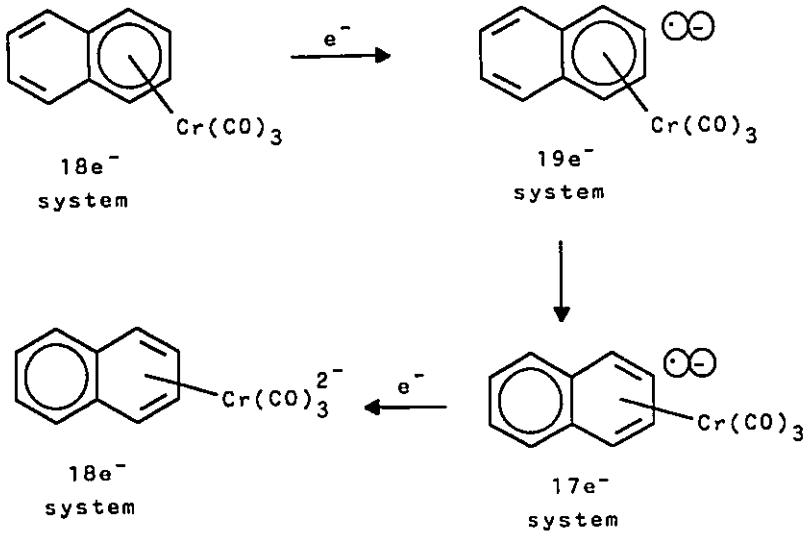


Figure 2: Reduction of chromium complexes with alkali metal

These η^4-complexes were able to undergo aerial oxidation and electrophilic attack on a ring carbon.[14] The number of electrophiles which have been found to undergo nucleophilic attack by a ring carbon of these η^4-complexes are small, consisting of CO_2, O_2 and $PhCH_2Cl$. The resulting anion could then be trapped by forming a salt, or could be allowed to undergo aerial oxidation to restore the η^6-complex with the electrophile substituted on the arene ring. **Figure 3** illustrates a typical reaction pathway for the formation of the dianion by reduction of the η^6-complex by potassium naphthalenide, and subsequent trapping with an electrophile. The limited attention which this chemistry has received is testament to the most common outcome of these reductions, which is decomplexation.

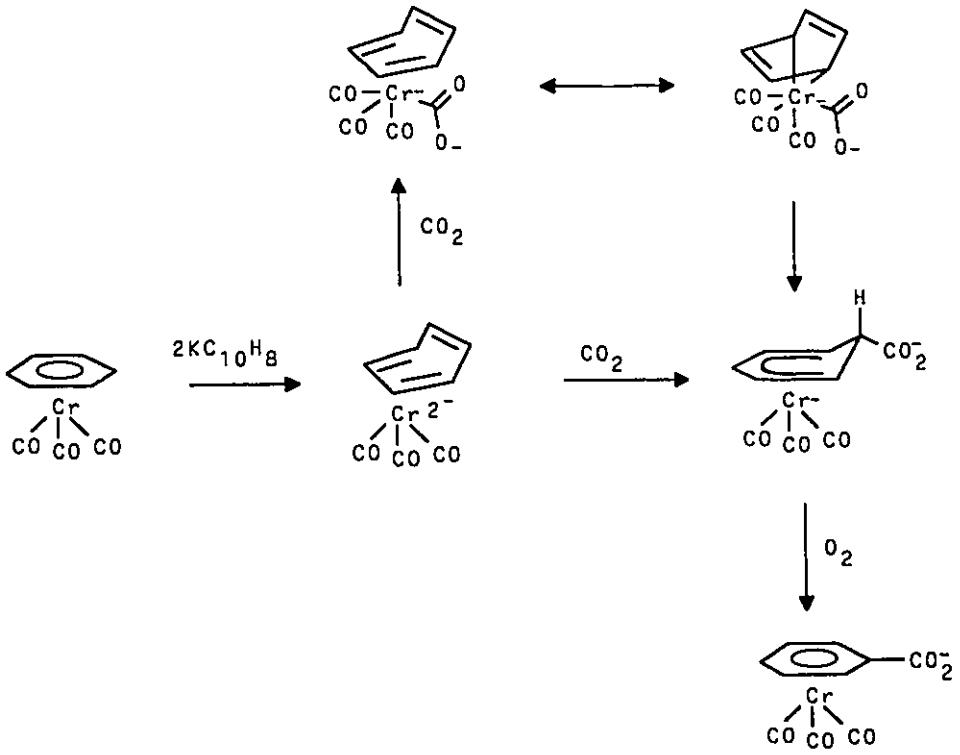
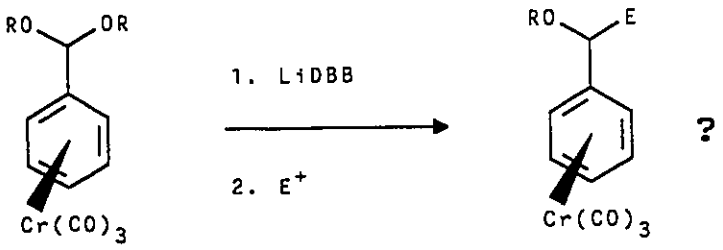


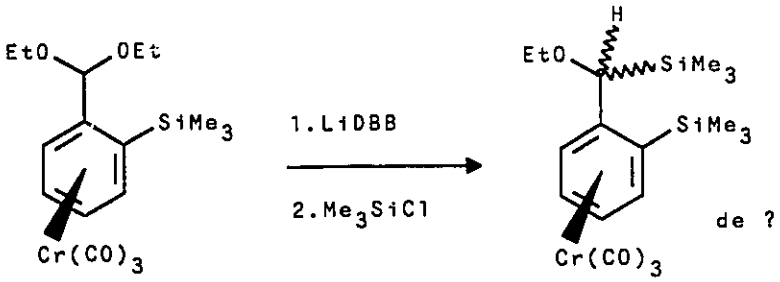
Figure 3: Reaction of chromium complex and potassium naphthalenide

While carrying out deprotonation reactions in **Chapter 1**, a curious side product was obtained which appeared to come from the reduction of the acetal function. A short experiment proved that the radical anion was responsible for the observed reduction. Taking a series of both cyclic and noncyclic acetals of benzaldehyde complexed to chromium and reducing them with LiDBB, followed by electrophilic quenching would be an important series of experiments. These reactions would reveal the nature of the reactivity which these complexes have towards a radical anion (**Scheme 11**).



Scheme 11

Furthermore, if the acetal function could in fact be reduced to the benzylic anion and electrophiles trapped, then perhaps this incorporation could be done stereoselectively. An experiment which would illustrate whether or not this could be accomplished is shown in **Scheme 12**.



Scheme 12

Results and Discussion

For **Chapter 2** of this thesis a variety of acetal substrates were reduced with LiDBB, and trapped with a number of electrophiles to yield the corresponding products. The substrates chosen for this work are shown in **Figure 4**. Two yields are indicated, reflecting that of the metal-free acetal preparation (**1a-4a**) and the second indicating the complexation yield (**1b-4b**). The acetals **1a**, **2a**, and **3a** were prepared as in **Chapter 1**. The acetal **4a** was prepared from benzaldehyde, pTsOH, 1,3-propanediol and the use of a Dean Stark apparatus. The complexations were easy to perform and were accomplished in respectable yields (73%-85%). The remaining acetal **5a**, was prepared by metallation of **2b** with ^{n}BuLi, and subsequent trapping with Me_3SiCl. This method gave an overall yield of 65% incorporation of the trimethylsilyl group, but only a 52% yield of the intended ortho isomer **5a**. The meta isomer made up the remainder of the obtained silylated product. Careful flash chromatography was performed to separate the two.

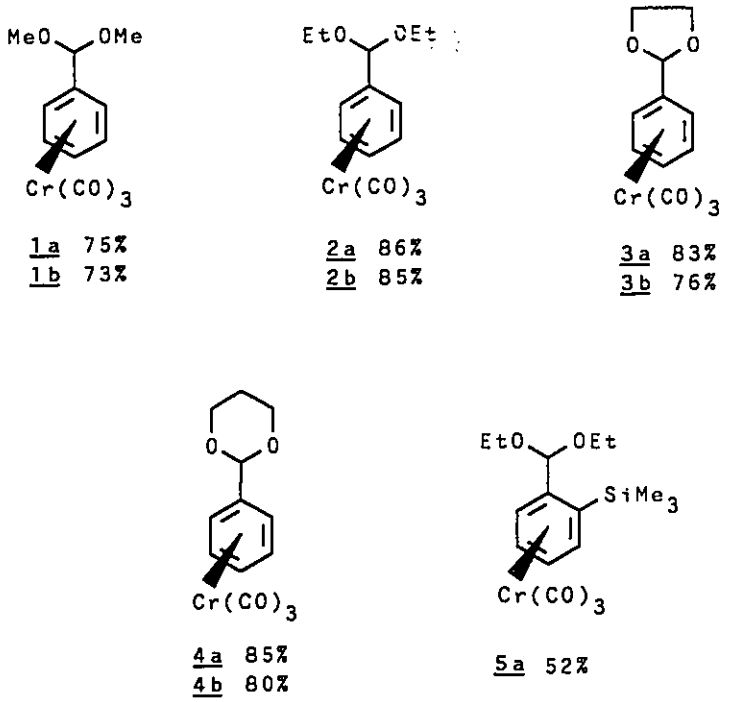


Figure 4: Acetal Substrates

The synthetic procedure for the reductions of the acetals required some optimization, as was the case in **Chapter 1** with the chiral alkyl chloride reductions. The lithium metal had to be freshly cut and quickly added to the reaction flask where it was then scratched in the THF/DBB solution with two syringe needles. The radical anion formation took place between -40 and -78 °C (anywhere in this range seemed to make no difference to the amount or speed of the radical anion formation). Initially the radical anion was allowed to form for 5-6 h in hopes of generating a full equivalent of LiDBB. This, however, was very difficult to do on a regular basis, so the acetal was added after only 1-2 h of anion formation, and its disappearance

followed by TLC. It normally took 1-2 h for the starting material to disappear, at which point the electrophile was added at -78 °C.

Table 1: Reduction Results

Entry	Substrate	Electrophile	Product	Yield (%) (de, %)
1	**2b**	Me_3SiCl	**6**	81
2	**2b**	CH_3I	**7**	63
3	**2b**	Acetone	**8**	43 + 26% **10**
4	**2b**	PhCHO	**9**	81
5	**2b**	H_2O	**10**	79
6	**2b**	$ClCO_2Me$	**11**	72
7	**2b**	Me_3SiCl[a]	**6**	52
8	**2b**	Me_3SiCl[b]	**NA**	0
9	**1b**	Me_3SiCl	**12**	69
10	**3b**	Me_3SiCl	**13**	76
11	**4b**	Me_3SiCl	**14**	78
12	**5a**	Me_3SiCl	**15a**	70.5 (88)

[a] 0.25 equivalents of DBB (Method B); [b] lithium metal only

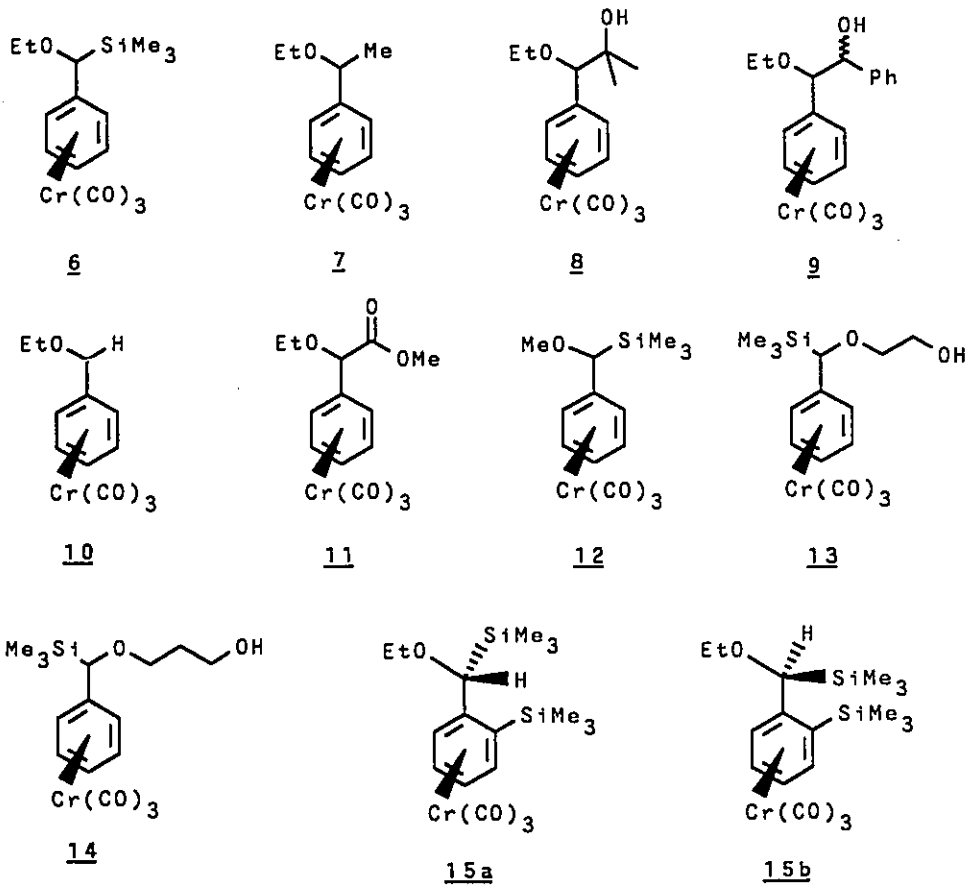
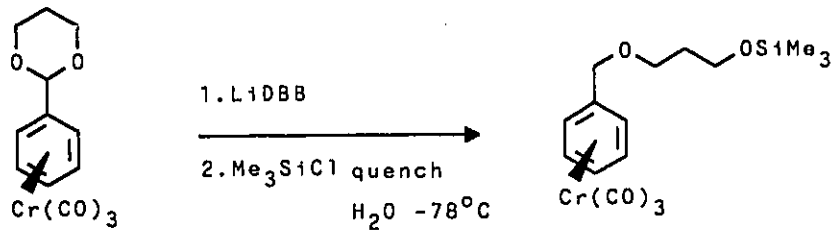


Figure 5: Reduction Products

As can be seen from **Table 1**, the yields for these reactions were quite respectable and the variety of acetals and electrophiles which can be employed is broad. In all cases there was never any observance of Wittig rearrangement products or the type of reaction products associated with the reduction to the η^4-complex. The results indicate that the radical anion exhibits no immediate tendency to decompose or decomplex these organometallic compounds. This in itself is very important, because it demonstrates that not only this type of reaction, but

radical anion methodology in general can be utilized in (arene)tricarbonylchromium chemistry without any ill effects to the complex.

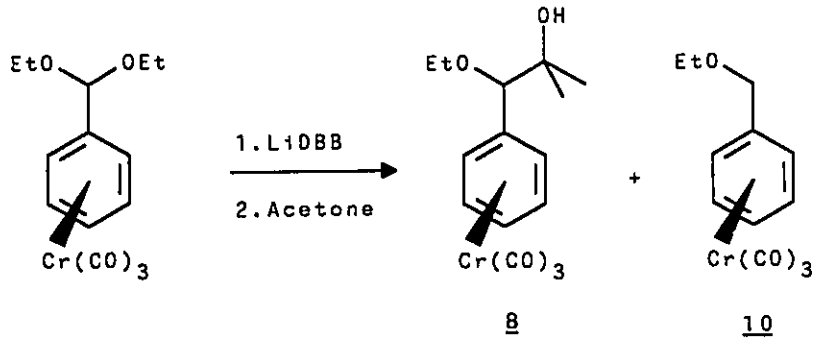
There does not appear (under the given reaction conditions), to be any preference as to whether cyclic or noncyclic acetals react with greater efficiency. It should be pointed out, however, that in the cases of the cyclic acetals, the liberated alkoxide anion is still part of the product. In the case of acetal **4b**, when Me_3SiCl was used as an electrophile (entry 11), it was necessary to let the reaction mixture warm to room temperature before adding water, and to employ mildly acidic conditions during workup (to hydrolyze the O-silyl group) in order to get the intended alcohol (**14**). If the mixture is quenched with water at -78 °C and the conditions for workup are too mild, the O-silylated compound **16** can be obtained in a yield as high as 72% (**Scheme 13**). This problem was not observed for the 1,3-dioxolane ring, which gave the intended product, **13**, under the usual reaction conditions.



4b **16**

Scheme 13

When acetone was used as the electrophile (entry 3), some insight as to the character of the benzyl anion was obtained. The anion appears to be mainly a nucleophile, but still has some ability to act as a base towards an enolizable carbonyl function. This was reflected in the formation of 10, the product of benzyl anion protonation, in substantial amounts (26%), in addition to the expected carbonyl attack product 8 (43%) (**Scheme 14**). It would be useful to find out what effect steric hinderance near the ketone function would have on the anion's ability to act as a base or nucleophile. Also, further work could be done with aldehydes and esters to see how they would fare as electrophiles in this chemistry.



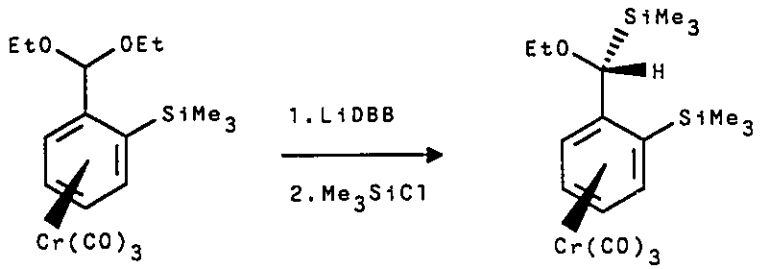
Scheme 14

Entry 7 shows the result of attempting the reaction in a catalytic fashion, where 0.25 equivalents of DBB was used with respect to the acetal. This attempt gave a modest 52% yield of the intended product, with the rest of the recovered material being uncharacterizable. The necessity for stoichiometric amounts of DBB is is not a problem, however, since the DBB is quantitatively recoverable for reuse.

It is also apparent that DBB is critical for this reaction, since when acetal **2b** was stirred with only freshly scratched lithium metal in THF for 4 h at -50 °C, and trapped with Me_3SiCl, no reaction took place. After workup the only isolated material was the starting substrate. This can be contrasted with the research by Azzena,[7] which had shown that the metal-free aryl acetals readily underwent reduction by lithium powder to yield the corresponding chromium-free products upon electrophile incorporation. Even though the present work did not involve the use of lithium powder, there still should have been sufficient surface area to at least give some reduction product. It seems then, that upon complexing the acetal to chromium, the reactivity of the acetal towards the bare alkali metal is reduced. Evidence to completely support or refute this argument would require carrying out numerous experiments of different temperatures with the acetal complex and lithium powder.

Finally, entry 12 demonstrates the potential for diastereoselection in these reductive lithiation reactions. Substrate **5a**, bearing an ortho trimethylsilyl function, underwent facile reaction with LiDBB at -78 °C. Subseqent incorporation of Me_3SiCl gave a 71% yield of **15a**, with the indicated diastereomer present in an 88% de (**Scheme 15**). This diastereoselection was slightly dissappointing, since the previously mentioned work by Davies[11] demonstrated that one diastereomer could be obtained with roughly 100% de by trapping benzylic anions which possessed a methoxy substituent in the ortho position. The bulk of the literature research reports are dominated by the use of an ortho methoxy substituent, and a case where a trimethylsilyl group was used could not be found to compare with the present work. The reason the trimethylsilyl group was chosen for this research was due to its size and because it is

removable with the use of fluoride ion.[15] The somewhat lower de's realized with the ortho trimethylsilyl substituent cannot be further rationalized at this point.



71%, 88% de

15a

Scheme 15

It was necessay to unambiguously prove that the tiny peaks in the ^{1}H NMR spectrum of **15a** were in fact due to the minor diastereomer (**15b**). To this end the original product **15a**, was subjected to light and air in an attempt to decomplex the arene fragment, the intention being to recomplex it to give a racemic mixture of the diastereomers. This decomplexation however, met with no success because the arene fragment could not be recovered intact and what was obtained could not be identified. Thus, an independant route was taken to prepare the compound without the chromium moiety, so that it could be complexed to give a mixture of the diastereomers. To this end, compound **20** was prepared via the route illustrated in **Figure 6**, involving carbonyl reduction to the alcohol (**17**), ether formation (**18**), silylation by metal-halogen exchange (**19**), and silylation by way of benzylic lithiation (**20**).

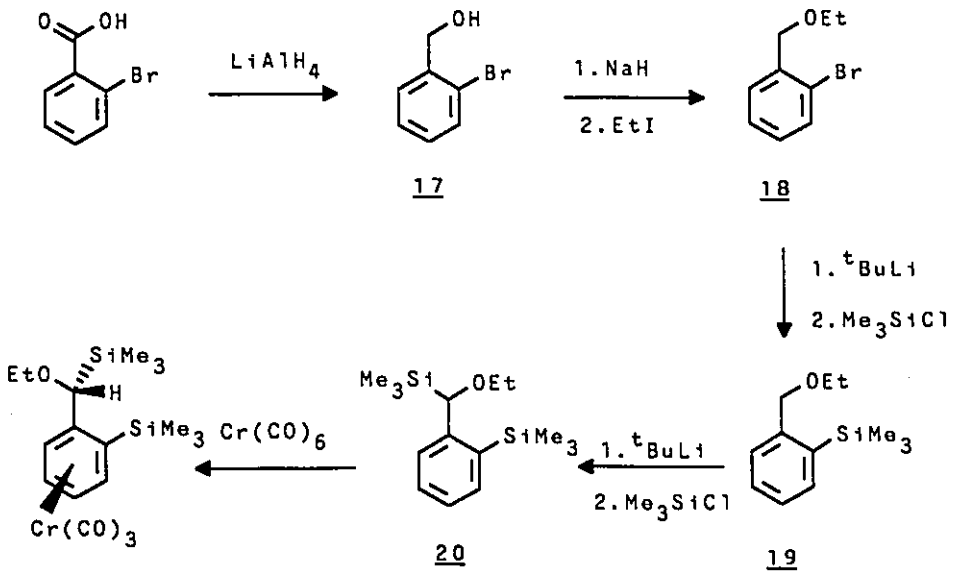
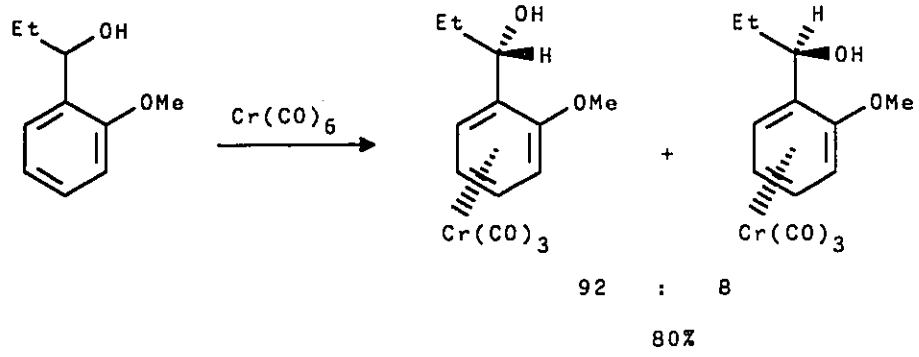


Figure 6: First attempt at mixture of 15a and 15b

Upon complexation of **20**, however, the product contained only one diastereomer. This diastereomer, having the same identity as the reductive lithiation product of **5a**, was obtained in such high purity that the absorptions due to the minor diastereomer which was originally being sought could not be found in the ^{1}H NMR! This was quite disturbing at first but it turns out that a related phenomenon is known. Uemura[16] has demonstrated that ortho disubstituted benzylic alcohols with a chiral center at the benzylic position where able to diastereoselectively complex to chromium under thermal conditions (**Scheme 16**). In the ethyl substituted case the de was only 84%, but in some other cases with different substituents at the benzylic position, de's of 100% were obtained, albeit, with a low yield (10%). Uemura was later able to get 100% de and 80-97% yield by using (naphthalene)$Cr(CO)_3$ as the complexing agent.



Scheme 16

Since the complexation of **20** clearly gave the thermodynamic diastereomer exclusively, a method was sought that would be better able to deliver the opposite stereoisomer. To this end, the silylation reaction of **6** was devised and carried out (**Figure 7**). Unfortunately, although good yields of the silylation product occurred, the only observable products were the meta and predominantly para substituted ones. Apparently, ortho lithiation of the complex with the benzylic trimethylsilyl group is sterically hindered to the point that it can not occur.

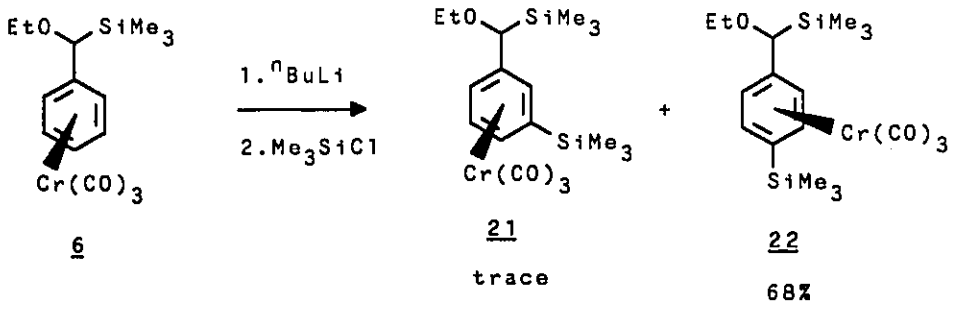


Figure 7: Second attempt at mixture of 15a and 15b

In order to identify the minor diastereomer in the reductive lithiation, the original reduction conditions (**Scheme 15**) were employed, except once the benzylic anion was formed it was warmed to -10 °C prior to the addition of the electrophile. Poor chemical yields of silylation resulted, but a tiny fraction turned out to be a 1:1 mixture of the two diastereomers (**Figure 8**), and the ^{1}H NMR spectrum could then be used to identify the minor diastereomer from **Scheme 15**. The main fraction of the product mixture was the ether complex **23** (50%); a fair amount of decomplexed material, as well as many unidentifiable fractions, also were present. It seems clear that this reaction requires a low temperature in order to operate properly.

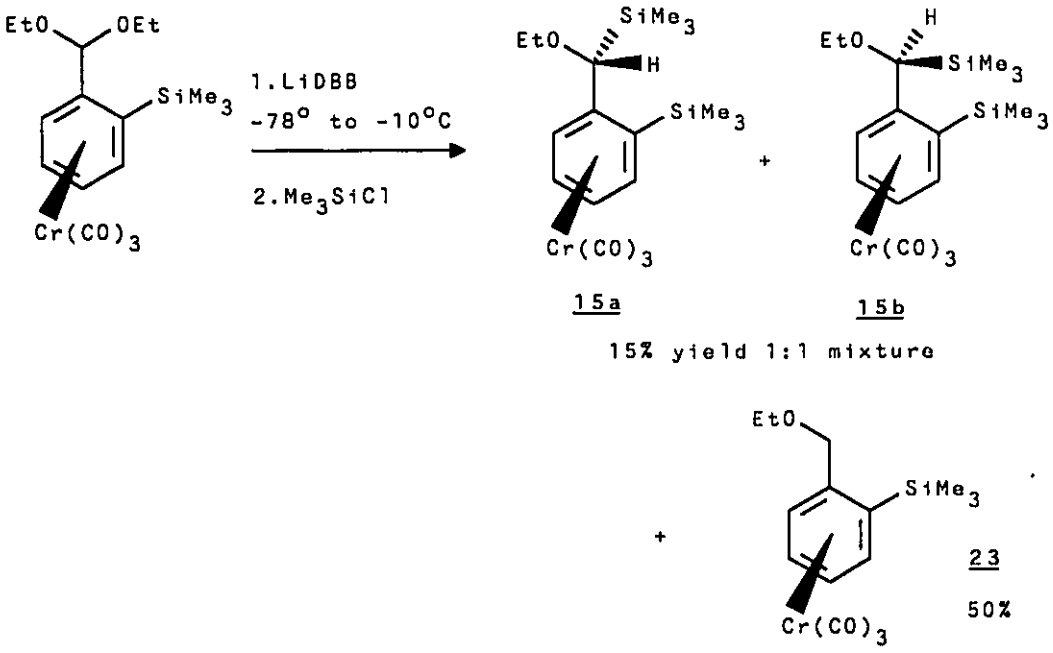
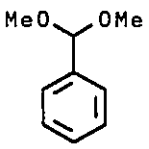


Figure 8: Preparation of 15a and 15b

In closing, a variety of (arene)tricarbonylchromium(0) acetal complexes have been shown to readily undergo reduction through the use of LiDBB. The resulting benzyl anion complexes can then be subjected to trapping with a number of electrophiles in respectable yields. In addition, a high level of diastereoselection at the benzylic site was observed for the case involving a complex which was ortho disubstituted. The work presented at this point is fairly straightforward and consequently there is little room for improvement of the reaction conditions. The future work which needs to be investigated lies in the applications of this methodology.

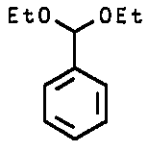
Experimental

The general methods for this experimental section are identical to that of **Chapter 1**. Some of the compounds in this Chapter have been reported in **Chapter 1**. These are indicated in the following text, and it must be noted that these compounds may have different numbers in this Chapter for simplicity.



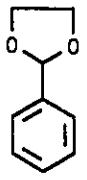
(Dimethoxy)methylbenzene (1a)

Refer to the procedure for compound **8** in the Experimental section of **Chapter 1.**



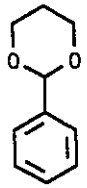
(Diethoxy)methylbenzene (2a)

Refer to the procedure for compound **10** in the Experimental section of **Chapter 1.**



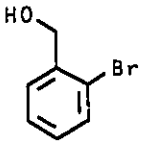
2-Phenyl-1,3-dioxolane (3a)

Refer to the procedure for compound **11** in the Experimental section of **Chapter 1.**



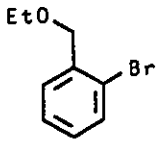
2-Phenyl-1,3-dioxane (4a)

The procedure was the same as that described for **3a**, except propane-1,3-diol was used instead of ethane-1,2-diol. The product was obtained in 85% yield and was recrystallized from hexane, mp 45-46 °C, (Lit. 48-49 °C).[17]



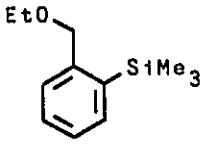
1-Bromo-2-(hydroxymethyl)benzene (17)

o-Bromobenzoic acid (5.0 g) was placed in a round-bottomed flask (250 mL) and dissolved in THF (100 mL). Borane-THF complex (2 equiv, 1.0M in THF) was added over 10 min, and then refluxed for 2 d. Aqueous workup yielded 4.43 g (95%) of the white crystalline product, mp 78-80 °C (ethanol), (Lit. 79-82 °C).[18]



1-Bromo-2-(ethoxymethyl)benzene (18)

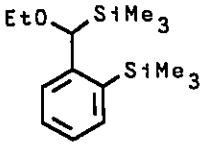
Sodium hydride (0.192 g; 60% dispersion in mineral oil) was placed in a three neck round-bottomed flask (150 mL), where it was washed twice with diethyl ether (15 mL). THF (20 mL) was then added, followed by the addition of bromobenzyl alcohol (17),(0.75 g) in THF (5 mL). This solution was stirred for 0.5 h at room temperature and then refluxed overnight. After cooling, water was added and the product obtained following a standard aqueous workup. Distillation yielded a clear liquid (81%), bp 70-75 °C/0.54 mm; IR (NaCl neat) 3109, 2974, 2867, 1123, 1102, 1026, ν_{max} 749 cm^{-1}; ^1H NMR, δ, 7.51 (d, 1H, J=7.9), 7.47 (d, 1H, J=7.7), 7.30 (t, 1H, J=7.6), 7.12 (t, 1H, J=7.6), 4.55 (s, 2H), 3.60 (q, 2H, J=6.9), 1.27 (t, 3H, J=6.9); ^{13}C NMR, δ, 138.1, 132.6, 129.0, 128.9, 127.5, 122.8, 72.0, 66.4, 15.3; MS m/e 214 (M^+); HRMS m/e for $C_9H_{11}BrO$ calcd. (M^+) 213.9993, found 213.9997.



1-(Ethoxymethyl)-2-trimethylsilylbenzene (19)

18 (2.92 g) was placed in a two neck flask (100 mL) with THF (25 mL) and cooled to -78 °C. ^{t}BuLi (2 equiv) was then added and the solution stirred for 1 h. Me_3SiCl (1.5 equiv) was added and the solution stirred overnight. After warming to room temperature, water was added and a typical aqueous workup performed to give the crude product. Distillation gave

1.95 g (74%) of a clear liquid, bp 135-139 °C/20 mm; IR (NaCl neat) 3125, 2972, 2963, 2865, 1247, 1098, ν_{max} 838 cm^{-1}; ^1H NMR, δ, 7.54 (d, 1H, J=8.7), 7.44 (d, 1H, J=7.3), 7.38 (t, 1H, J=7.3), 7.26 (t, 1H, J=7.4), 4.58 (s, 2H), 3.58 (q, 2H, J=7.0), 1.28 (t, 3H, J=7.0), 0.35 (s, 9H); ^{13}C NMR, δ, 143.9, 138.5, 134.8, 129.3, 128.5, 127.0, 73.2, 66.0, 15.4, 0.4; MS m/e 208 (M^+); HRMS m/e for $C_{12}H_{20}OSi$ calcd. (M^+) 208.1283, found 208.1284.

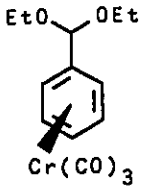


1-(Ethoxytrimethylsilyl)methyl-2-trimethylsilylbenzene (20)

19 (0.5 g) was placed in a round-bottomed flask (100 mL) with THF (10 mL) and cooled to -78 °C. ^{t}BuLi (1.1 equiv) was added and the solution stirred for 1 h. Me_3SiCl (1.5 equiv) was then added and the solution stirred overnight while it warmed to room temperature. An aqueous workup was then carried out and the crude product distilled to give **20** (0.481 g, 71%) of a clear liquid, bp 85-90 °C/0.29 mm; IR (NaCl neat) 3054, 2957, 2896, 2862, 1248, 1115, ν_{max} 840 cm^{-1}; ^1H NMR, δ, 7.46 (d, 1H, J=7.2), 7.42 (d, 1H, J=7.6), 7.35 (t, 1H, J=7.9), 7.17 (t, 1H, J=7.5) 4.39 (s, 1H), 3.47 (m, 1H), 3.32 (m, 1H), 1.15 (t, 3H, J=7.0), 0.34 (s, 9H), -0.01 (s, 9H); ^{13}C NMR, δ, 148.8, 136.6, 134.5, 129.2, 126.4, 125.3, 76.7, 66.1, 15.9, 1.6, -3.0; MS m/e 280 (M^+); HRMS m/e for $C_{15}H_{28}OSi_2$ calcd. (M^+) 280.1678, found 280.1679.

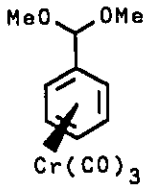
Preparation of η^6-(arene)tricarbonylchromium(0) complexes

Refer to the general procedure for the preparation of (η^6-arene)tricarbonylchromium(0) complexes given in Experimental section of **Chapter 1**.



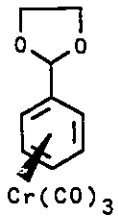
[η^6-(Diethoxymethyl)benzene]tricarbonylchromium (0) (2b)

Refer to the procedure for compound **14** in the Experimental section of **Chapter 1.**



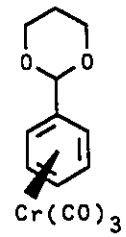
[η^6-(Dimethoxymethyl)benzene]tricarbonylchromium (0) (1b)

Refer to the procedure for compound **12** in the Experimental section of **Chapter 1.**



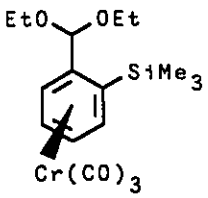
[η⁶-2-Phenyl-1,3-dioxolane]tricarbonylchromium (0) (3b)

Refer to the procedure for compound **15** in the Experimental section of **Chapter 1.**



[η⁶-2-Phenyl-1,3-dioxane]tricarbonylchromium (0) (4b)

Yellow crystals were obtained in 80% yield, mp 106-107 °C (pentane/ether), (Lit. 106-109 °C).[19]

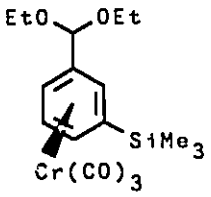


[η⁶-1-(Diethoxymethyl)-2-trimethylsilylbenzene]tricarbonylchromium (0) (5a)

2b (0.52 g) was placed in a 100 mL two-neck round-bottomed flask under nitrogen with of dry THF (20 mL). Butyllithium (1.1 equiv) was then added at -78 °C and the solution was stirred for 1 h at which time Me_3SiCl (2 equiv) was added. The solution was stirred for 1 h,

quenched with water, and extracted in the usual way. Column chromatography with petroleum ether:EtOAc (5:1) yielded the intended **5a** in 52% yield. An additional 13% yield resulted from the meta isomer (**5b**).

Yellow crystals, mp 57-59 °C (pentane); IR (KBr pellet) 1959, 1874 cm^{-1}; ^1H NMR, δ, 5.64 (d, 1H, J=6.5), 5.56 (t, 1H, J=6.3), 5.39 (d, 1H, J=7.0), 5.37 (s, 1H), 5.16 (t, 1H, J=6.1), 3.34-3.80 (four multiplets, 4H), 1.27 (t, 3H, J=7.1), 1.15 (t, 3H, J=7.1), 0.35 (s, 9H); ^{13}C NMR, δ, 233.2, 114.3, 100.1, 98.5, 94.3, 91.1, 89.8, 89.7, 64.8, 58.0, 15.2, 15.1, 0.6; MS m/e 388 (M^+); Anal. Calcd. for $C_{17}H_{24}CrO_5Si$: C, 52.58; H, 6.19. Found: C, 52.42; H, 6.14.



[η⁶-1-(Diethoxymethyl)-3-trimethysilybenzene]tricarbonylchromium (0) (5b)

Viscous yellow oil, IR (neat, NaCl) 1966, 1888 cm^{-1}; ^1H NMR, δ, 5.75 (d, 1H, J=6.5), 5.64 (s, 1H), 5.39 (d, 1H, J=6.1), 5.16 (t, 1H, J=6.3), 5.09 (s, 1H), 3.64 (m, 4H), 1.24 (m, 6H), 0.28 (s, 9H); ^{13}C NMR, δ, 232.9, 106.0, 100.3, 99.5, 98.5, 98.1, 94.3, 89.6, 62.9, 62.5, 15.2, -1.1; MS m/e 388 (M^+); Anal. Calcd. for $C_{17}H_{24}CrO_5Si$: C, 52.58; H, 6.19. Found: C, 52.39; H, 6.29.

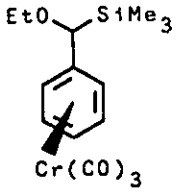
Procedure for acetal reductions

Method A:

DBB (0.15-0.20 g) was stirred with a dime sized chunk of freshly scratched lithium metal in THF (10 mL) at -78 °C in a round-bottomed flask (100 mL) under argon for 1-2 h. The substrate acetal (50-100 mg) was then added in THF (1.0 mL) and the solution stirred until TLC showed no more starting material. The appropriate electrophile (1.5 equiv) was then added, and the solution stirred for 1 h and quenched with water. A typical workup afforded the crude product.

Method B:

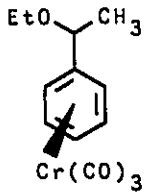
DBB (0.25 equiv with respect to the substrate acetal), a dime sized chunk of freshly scratched lithium metal, and the substrate acetal (50-100 mg) were stirred in THF (10 mL) at -78 °C in a round-bottomed flask (100 mL) under argon until TLC showed no starting material. The appropriate electrophile (1.5 equiv) was then added, and the solution stirred for 1 h and quenched with water.A typical workup afforded the crude product.



[η⁶-(Ethoxytrimethylsilylmethyl)benzene]tricarbonylchromium (0) (6)

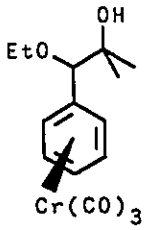
Method A was employed using substrate **2b** (52 mg) with Me_3SiCl as the electrophile. Column chromatography using petroleum ether:ether (10:1) afforded **6** (45.8 mg, 81%), mp 82-83 °C (pentane); IR (KBr pellet) 1965, 1902, 1855 cm^{-1}; ^1H NMR, δ, 5.54 (m, 1H), 5.30 (m, 2H), 5.23 (m, 1H), 5.05 (d, 1H, J=6.1), 4.02 (m, 1H), 3.73 (s, 1H), 3.50 (m, 1H), 1.21 (t, 3H, J=6.8), 0.00 (s, 9H); ^{13}C NMR, δ, 233.7, 113.7, 93.0, 91.6, 91.2, 90.3, 89.8, 75.0, 67.9, 15.7, -3.8; MS m/e 344 (M^+); Anal. Calcd. for $C_{15}H_{20}CrO_4Si$; C, 52.31; H, 5.85. Found C, 52.12; H, 6.03.

Method B was employed using substrate **2b** (100 mg) with Me_3SiCl as the electrophile followed by column chromatography using petroleum ether:ether (10:1) afforded **6** (57 mg, 52%).



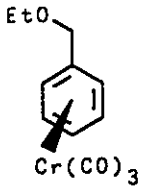
[η⁶-(1-Ethoxyethyl)benzene]tricarbonlychromium (0) (7)

Method A was employed using substrate **2b** (65 mg) with CH_3I as the electrophile. Column chromatography using petroleum ether:ether (10:1) afforded **7** (37 mg, 63%); IR (neat, NaCl) 1971, 1963, 1874 cm^{-1}; ^1H NMR, δ, 5.54 (m, 1H), 5.30 (m, 4H), 4.12 (q, 1H, J=6.4), 3.62 (br m, 2H), 1.41 (d, 3H, J=6.4), 1.22 (t, 3H, J=7.0); ^{13}C NMR, δ, 233.0, 113.9 92.9, 92.0, 91.55, 91.49, 91.3, 75.2, 65.2, 23.0, 15.5; MS m/e 286 (M^+); HRMS m/e for $C_{13}H_{14}CrO_4$ calcd (M^+) 286.0297, found 286.0290.



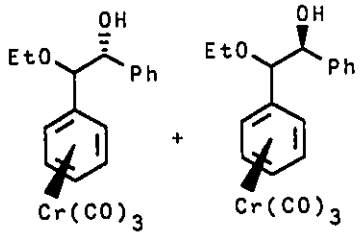
[η⁶-(1-Ethoxy-2-hydroxy-2-methylpropyl)benzene]tricarbonylchromium (0) (8)

Method A was employed using substrate **2b** (60 mg) with acetone as the electrophile. Column chromatography using petroleum ether:ether (10:1) afforded **8** (22 mg, 43%) and **10** (16 mg, 26%); IR (neat, NaCl) 3412, 1964, 1879 cm^{-1}; ^1H NMR, δ, 5.73 (d, 1H, J=6.5), 5.45 (t, 1H, J=6.3), 5.38 (d, 1H, J=6.6), 5.21 (t, 1H, J=6.2), 5.13 (t, 1H, J=6.3), 4.06 (m, 1H), 3.68 (s, 1H), 3.64 (m, 1H), 2.21 (s, 1H, exchangeable), 1.28 (t, 3H, J=7.0), 1.18 (s, 3H), 1.10 (s, 3H); ^{13}C NMR, δ, 233.1, 107.0, 95.7, 95.4, 93.5, 89.5, 89.0, 85.8, 73.5, 68.0, 25.9, 25.5, 15.5; MS m/e 330 (M^+); Anal. Calcd for $C_{15}H_{18}CrO_5$: C, 54.54; H, 5.45. Found: C, 54.66; H, 5.53.



[η⁶-(Ethoxymethyl)benzene]tricarbonylchromium (0) (10)

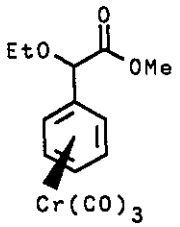
Method A was employed using substrate **2b** (61 mg) with H_2O as the electrophile. Column chromatography using petroleum ether:ether (10:1) afforded **10** (41 mg, 79%) IR (neat, NaCl) 1964, 1879 cm^{-1}; ^1H NMR, δ, 5.34 (m, 4H), 5.24 (m, 1H), 4.18 (s, 2H), 3.59 (q, 2H, J=7.0), 1.23 (t, 3H, J=7.0); ^{13}C NMR, δ, 232.8, 108.2, 93.0, 92.3, 91.5, 71.1, 66.9, 15.2; MS m/e 272 (M^+); HRMS m/e for $C_{12}H_{12}CrO_4$ calcd (M^+) 272.0140, found 272.0136.



[η⁶-(1-Ethoxy-2-hydroxy-2-phenylethyl)benzene]tricarbonylchromium (0) (9)

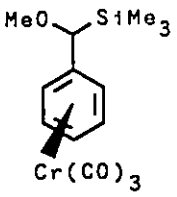
Method A was employed using substrate **2b** (34 mg) with PhCHO as the electrophile. Column chromatography using petroleum ether:ether (10:1) afforded **9** (33 mg, 81%), mp 91-94 °C (petroleum ether/Et_2O); IR (KBr pellet) 3443, 1965, 1881 cm^{-1}; ^1H NMR, δ, major

diastereomer 7.1-7.35 (m, 5H), 5.60 (t, 1H, J=6.6), 5.10-5.38 (m, 2H), 4.94 (m, 1H), 4.61 (d, 1H, J=6.5), 4.53 (dd, 1H), 3.90-4.15 (m, 2H), 3.59 (m, 1H), 3.08 (d, exchangeable, 1H, J=3.6), 1.27 (m, 3H); minor diastereomer 5.26 (d, 1H, J=6.1), 3.85 (m, 1H), 2.50 (d, exchangeable, 1H, J=3.2); ^{13}C NMR, δ, 232.8, 138.9, 128.2, 128.1, 127.3, 106.8, 94.7, 94.06, 92.1, 90.0, 89.4, 84.2, 78.8, 67.5, 15.34; minor diastereomer 233.0, 139.1, 128.3, 128.0, 126.7, 107.0, 94.01, 92.7, 90.5, 89.7, 83.2, 76.1, 67.0, 15.28, MS m/e 378 (M^+); Anal. Calcd for $C_{19}H_{18}CrO_5$: C, 60.31; H, 4.76. Found: C, 60.50; H, 4.82.



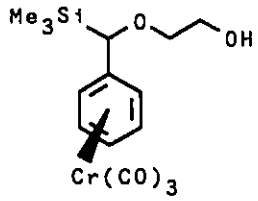
[η^6-(Carbomethoxyethoxymethyl)benzene]tricarbonylchromium (0) (11)

Method A was employed using substrate **2b** (78 mg) with $ClCO_2Me$ as the electrophile. Column chromatography using petroleum ether:ether (10:1) afforded **11** (59 mg, 72%), IR (neat, NaCl) 1966, 1881, 1750 cm^{-1}; ^{1}H NMR, δ, 5.63 (d, 1H, J=6.0), 5.55 (d, 1H, J=6.2), 5.27 (m, 3H), 4.48 (s, 1H), 3.78 (s, 3H), 3.72 (m, 1H), 3.61 (m, 1H), 1.28 (t, 3H, J=7.0); ^{13}C NMR, δ, 232.3, 170.4, 106.0, 93.0, 92.3, 91.8, 90.9 (two resonances, overlap), 78.7, 67.1, 52.7, 15.1; MS m/e 330 (M^+); HRMS m/e for $C_{14}H_{14}CrO_6$ calcd. (M^+) 330.0195, found 330.0184.



[η⁶-(Methoxytrimethylsilylmethyl)benzene]tricarbonylchromium (0) (12)

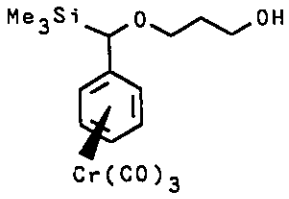
Method A was employed using substrate **1b** (40 mg) with Me_3SiCl as the electrophile. Column chromatography using petroleum ether:ether (10:1) afforded **12** (32 mg, 69%), mp 70-71 °C (petroleum ether); IR (KBr pellet) 1964, 1874, 846 cm^{-1}; ^1H NMR, δ, 5.48 (d, 1H, J=5.9), 5.29 (m, 3H), 5.03 (d, 1H, J=6.2), 3.58 (s, 3H), 0.01 (s, 9H); ^{13}C NMR, δ, 233.6, 113.1, 92.7, 91.8, 91.4, 90.0, 89.2, 77.4, 60.7, -3.79; MS m/e 330 (M^+); Anal. Calcd for $C_{14}H_{18}CrO_4Si$: C, 50.90; H, 5.45. Found: C, 50.67; H, 5.55.



[η⁶-((2-Hydroxyethoxy)trimethylsilylmethyl)benzene]tricarbonylchromium (0) (13)

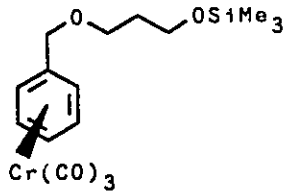
Method A was employed using substrate **3b** (100 mg) with Me_3SiCl as the electrophile. Column chromatography using petroleum ether:ether (10:1) afforded **13** (96 mg, 76%), mp 62-65 °C (petroleum ether/ether); IR (KBr pellet) 3452, 1948, 1877 cm^{-1}; ^1H NMR, δ, 5.51 (m, 1H), 5.32 (m, 2H), 5.24 (m, 1H), 5.05 (d, 1H, J=6.42), 4.13 (m, 1H), 3.82 (s, 2H), 3.77 (br s, 1H), 3.59 (m, 1H), 1.88 (s, 1H), 0.03 (s, 9H); ^{13}C NMR, δ, 233.6, 112.6, 93.1, 91.7,

91.3, 90.3, 89.5, 75.8, 73.6, 62.5, -3.7; MS m/e 360 (M^+); Anal. Calcd for $C_{15}H_{20}CrO_5Si$: C, 50.00; H, 5.55. Found: C, 49.86; H, 5.66.



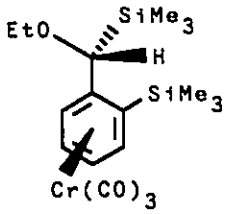
[η⁶-((3-Hydroxypropoxy)trimethylsilylmethyl)benzene]tricarbonylchromium (0) (14)

Method A was employed using substrate **4b** (82 mg) with Me_3SiCl as the electrophile. To obtain the intended product it was necessary to let the reaction warm to room temperature and quench with 3M HCl. Column chromatography using petroleum ether:ether (10:1) afforded **14** (79 mg, 78%); IR (neat, NaCl) 3384, 1962, 1875, 843 cm^{-1}; ^1H NMR, δ, 5.47 (m, 1H), 5.32 (m, 2H), 5.24 (m, 1H), 5.04 (m, 1H), 4.25 (m, 1H), 3.81 (m, 2H), 3.75 (s, 1H), 3.58 (m, 1H), 2.06 (br s, 1H exchangeable), 1.89 (m, 2H), 0.02 (s, 9H); ^{13}C NMR, δ, 233.5, 112.8, 93.0, 91.7, 91.2, 90.2, 89.3, 76.1, 71.4, 61.8, 32.9, -3.8; MS m/e 374 (M^+); HRMS m/e calcd for $C_{16}H_{22}CrO_5Si$ (M^+) 374.0641, found 374.0629.



[η^6-(3-Trimethylsilyloxypropoxymethyl)benzene]tricarbonylchromium (0) (16)

Method A was employed using substrate **4b** (95 mg) with Me_3SiCl as the electrophile. Column chromatography using petroleum ether:ether (10:1) afforded **16** (85 mg, 72%) as an oil; IR (neat, NaCl) 1968, 1883, 841 cm^{-1}; ^1H NMR, δ, 5.33 (m, 4H), 5.24 (m, 1H), 4.18 (s, 2H), 3.58-3.69 (two overlapping t, 4H), 1.81 (m, 2H), 0.09 (s, 9H); ^{13}C NMR, δ, 232.7, 108.2, 92.8, 92.1, 91.5, 71.3, 68.1, 59.3, 32.7, -0.4; MS m/e 374 (M^+); HRMS m/e calcd for $C_{16}H_{22}CrO_5Si$ (M^+) 374.0641, found 374.0653.



[η^6-1-(Ethoxytrimethylsilylmethyl)-2-trimethylsilylbenzene]tricarbonylchromium (0) (15a)

Method A was employed using substrate **5a** (52 mg) with Me_3SiCl as the electrophile. Column chromatography using petroleum ether:ether (10:1) afforded **15a** (39 mg, 71%); IR (neat, NaCl) 1962, 1881 cm^{-1}; ^1H NMR, δ, 5.48 (t, 1H, J= 6.3), 5.28 (d, 2H, J=5.9), 5.18 (t,

1H, J=6.3), 3.89 (m, 1H), 3.87 (s, 1H), 3.51 (m, 1H), 1.20 (t, 3H, J=6.9), 0.38 (s, 9H), 0.00 (s, 9H); ^{13}C NMR, δ, 233.7, 124.1, 99.0, 97.4, 93.5, 91.7, 88.4, 73.8, 67.8, 15.6, 1.9, -2.4; MS m/e 416 (M^+); HRMS m/e calcd for $C_{18}H_{28}CrO_4Si_2$ (M^+) 416.0931, found 416.0938. Integration of the Me_3Si absorptions in the ^1H NMR spectrum indicated an 88% de (94:6 ratio).

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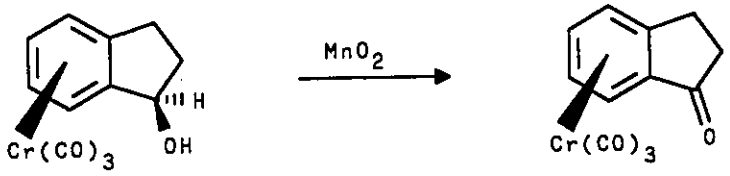
Apppendix A: Oxidation of Non-benzylic (Hydroxyarene)tricarbonylchromium Complexes

Introduction

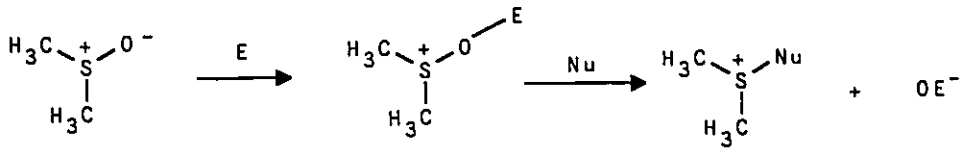
Although (arene)tricarbonylchromium(0) complexes can undergo many common synthetic transformations, oxidations of non-benzylic alcohols to their carbonyl analogues have not been successfully accomplished. The more reactive benzylic alcohols have been oxidized by MnO_2,[1] and by acetic anhydride-DMSO[2] conditions. It is noteworthy that these reagents fail completely to oxidize non-benzylic (hyrdroxyarene)tricarbonylchromium complexes. Jaouen et al were able to take the chromium complexes of indanols and tetralols and successfully oxidized them using MnO_2 to their corresponding indanones and tetralones in yields of approximately 70% **(Scheme 1)**.



Scheme 1

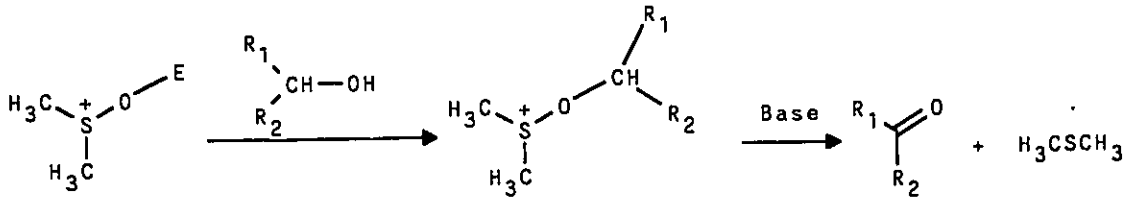
Levine et al were able to improve the yields of these reactions to 77% by using a mixture of acetic anhydride and DMSO. This latter reagent is a member of a class of oxidants called 'activated DMSO' reagents .[3] The nature of this activation stems from

electrophilic attack on the oxygen atom of DMSO, which renders subsequent nucleophilic attack on the sulphur atom by an alcohol function more facile (**Scheme 2**).



Scheme 2

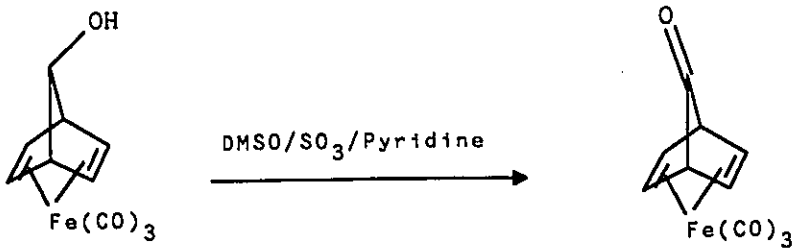
Reagents which are capable of activating DMSO in this manner include trifluoroacetic anhydride, thionyl chloride, oxalyl chloride, t-butyl hypochlorite, chlorine-acetic anhydride, acetyl chloride, benzoyl methanesulfonyl- and toluenesulfonyl chlorides, carbonochloridates, sulfur trioxide/pyridine, trifluoromethanesulfonic anhydride, dicyclohexylcarbodiimide, phosphorus pentoxide, polyphosphoric acid, bromine, ethoxyacetylene, and diphenylketen-N-p-tolylimine.[3] Aside from the aforementioned alcohols, phenols, enols, amines and oximes are possible nucleophiles. A general pathway for the oxidation of an alcohol is given in **Scheme 3**.



Scheme 3

Since typical oxidizing reagents such as the Jones reagent ($CrO_3/H_2SO_4/H_2O$/acetone) or the Swern reagent (DMSO/oxalyl chloride/triethylamine)

cause the tricarbonylchromium fragment to be lost from the arene fragment, a set of conditions which can oxidize nonbenzylic alcohol functions and leave the complex intact would be useful. In particular, it is thought that the failure of the Swern oxidation conditions stems from the presence of chloride ion, as halide ions present in either Lewis or Bronstead acidic form often rapidly decompose (arene)tricarbonylchromium complexes.[4] Of the other activated reagents, the DMSO/Sulfur trioxide/pyridine mixture is able to oxidize tricarbonyl[7-norbornadienol]iron to tricarbonyl[7-norbornadienone]iron without decomplexation (**Scheme 4**). The success which this reagent displayed in this instance gives a certain measure of confidence that this same reagent could work well on other metal carbonyl complexes.

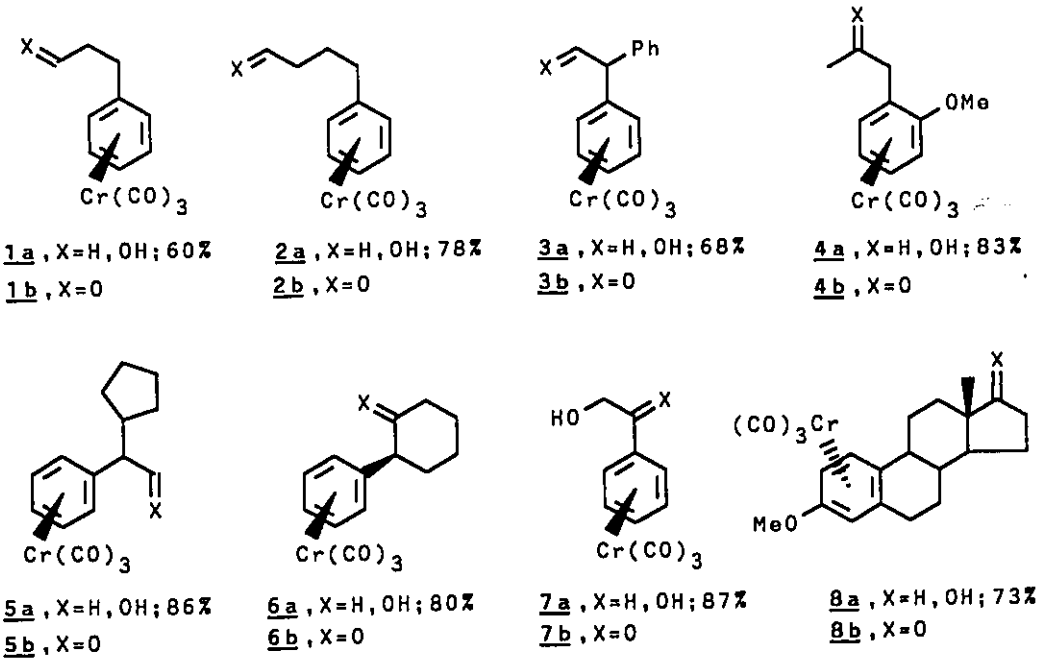


Scheme 4

In addition, DMSO/TFAA (trifluoroacetic anhydride) is a halide free oxidant which has a demonstrated effectiveness for many alcohol to carbonyl oxidations at low temperatures. Therefore these two reagents were chosen for this study in the oxidations of (hydroxyarene)tricarbonylchromium complexes.

Results and Discussion

In order to examine the effectiveness of these two reagents, several non-benzylic (hydroxyarene)tricarbonylchromium complexes were prepared, as well as a diol which would give rise to a competition between the benzylic and non-benzylic site. To this end the alcohols in **Figure 1** were prepared in the yields shown. The experiments involved in this research were a joint effort between Dr. Jim Green (experiments on chloride ion effects and reagent equivalent optimizations), Kevin M. McKay (compounds **5-8**), and this author (compounds **1-4**), with all of the results included here for completeness sake. These complexes were prepared in respectable yields, by the method given in the experimental,and were easily purified by column chromatography.



1a, X=H,OH; 60%
1b, X=O

2a, X=H,OH; 78%
2b, X=O

3a, X=H,OH; 68%
3b, X=O

4a, X=H,OH; 83%
4b, X=O

5a, X=H,OH; 86%
5b, X=O

6a, X=H,OH; 80%
6b, X=O

7a, X=H,OH; 87%
7b, X=O

8a, X=H,OH; 73%
8b, X=O

Figure 1:Oxidation substrates and products

The DMSO/SO_3/pyridine oxidations were performed by adding the substrate to the reagent at 0 °C, followed by warming to room temperature for 0.5 h. Using these conditions, it was found that 5 equivalents of reagent were necessary to give complete oxidation. The DMSO/TFAA reagent is not stable above -30 °C, so consequently the preparation of this reagent and the oxidations were performed at -78 °C. With this reagent, 2.5 equivalents gave optimal results for the oxidations, while using greater than 3 equivalents lead to significant amounts of decomplexation.

The results for the oxidations of the alcohols **1a-8a**, by both reagents, are given in **Table 1**. In all cases, respectable amounts of the corresponding carbonyl compound, whether ketone or aldehyde, were observed. The efficiency with which the two reagents carried out the oxidations was generally the same, except for the diol **7a**, which was oxidized much more selectively with the SO_3/pyridine reagent. Both reagents oxidized the benzylic site preferentially to give the corresponding ketone.

There were two minor side products which accompanied these oxidations, one being the formation of methylthiomethyl ether and the other being decomplexation of the arene. The decomplexation occurred in only trace amounts when either reagent was used properly, but became substantial (ca. 20%), with DMSO/TFAA if the stoichiometry of this reagent were not carefully controlled. The methylthiomethyl ethers accounted for ≤10% of the crude reaction product in the oxidations of primary alcohols **1a** and **2a**, as indicated by the ^{1}H NMR spectra (singlet at ~4.6 ppm).

Table 1: Oxidation Results

Entry	*Alcohol*	*Product*	*Yield (%) TFAA*	*Yield (%) SO_3/pyridine*
1	**1a**	**1b**	80	75
2	**2a**	**2b**	73	76
3	**3a**	**3b**	72	71
4	**4a**	**4b**	80	81
5*	**5a**	**5b**	75	72
6*	**6a**	**6b**	64	60
7**	**7a**	**7b**	61	85
8*	**8a**	**8b**	61	61

* These entries were completed by fellow coworker Kevin M. McKay; ** Joint Kevin M. McKay and Michael Siwek effort.

In an attempt to illustrate whether or not halide ion does in fact increase the amount of decomplexation, various sources of halide ion (LiI, $ZnCl_2$, $SnCl_4$) were added (equimolar to the oxidizing reagent) to each reagent mixture, prior to the addition of the alcohol **1a**, and the oxidation reactions conducted in the usual manner. For the reactions involving DMSO/SO_3/pyridine, the extent of decomplexation was about one third, while for the reagent of DMSO/TFAA the extent was roughly one half (extent of decomplexation was determined by integration of the complexed and uncomplexed aromatic regions in the ^{1}H NMR spectra of the crude reaction products). It is therefore

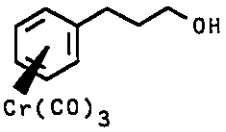
quite evident that the presence of halide ion is a source of decomplexation, although a mechanism for this cannot be given at this time.

In closing, two reagents have been found to successfully oxidize (hydroxyarene)tricarbonylchromium complexes, with structural variety, in respectable yields. Side reactions such as decomplexation or formation of methylthiomethyl ether are almost nonexistent.

Experimental

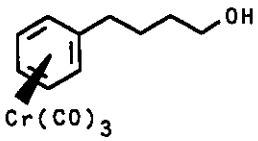
The experiemental presented here is comprised only of the compounds which were prepared for this thesis

The general methods for this experimental section are identical to those of **Chapter 1**



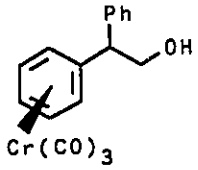
[(3-Hydroxypropyl)benzene]tricarbonylchromium (0) (1a)

Yellow crystals were obtained in 60% yield, mp 74-75 °C (petroleum ether/Et_2O); Lit 74.9-76.1 °C (toluene).[5]



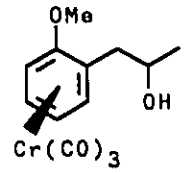
[(4-Hydroxybutyl)benzene]tricarbonylchromium (0) (2a)

A yellow oil was obtained in 78% yield; IR (NaCl neat) ν_{max} 3363 (br), 1961, 1868 cm^{-1}; ^1H NMR, δ, 5.37 (apparent t, 2H, J=6.5), 5.18 (m, 3H), 3.65 (m, 2H), 2.38 (t, 2H, J=7.3), 1.55-1.70 (m, 5H); ^{13}C NMR, δ, 233.3, 113.8, 94.1, 92.7, 90.6, 62.4, 34.9, 32.1, 27.5; MS m/e 286 (M^+); HRMS m/e calcd. for $C_{13}H_{14}CrO_4$ (M^+) 286.0297, found 286.0289.



[(2-Hydroxy-1-phenylethyl)benzene]tricarbonylchromium (0) (3a)

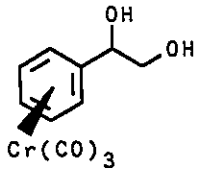
Yellow crystals were obtained in 68% yield; mp 75-78 °C (petroleum ether/ether); IR (KBr pellet) ν_{max} 3400 (br), 1960, 1868 cm^{-1}; ^1H NMR, δ, 7.2-7.5 (m, 5H), 5.66 (m, 1H), 5.33 (m, 2H), 5.20 (m, 1H), 5.16 (m, 1H), 4.06 (m, 2H), 3.85 (t, 1H, J=6.0), 2.21 (br.s, 1H); ^{13}C NMR, δ, 233.2, 139.7, 129.1, 128.8, 127.8, 113.1, 95.0, 93.8, 93.2, 92.4, 91.9, 65.8, 51.5; MS m/e 334 (M^+); HRMS m/e for $C_{17}H_{14}CrO_4$ calcd. (M^+) 334.0297, found 334.0289.



[1-(2-Hydroxypropyl)-2-methoxybenzene]tricarbonylchromium (0) (4a)

Yellow crystals were obtained as a mixture of diastereomers in 83% yield, mp 73-76 °C (petroleum ether/ether); IR (KBr pellet) ν_{max} 3385, 1968, 1953, 1865 cm^{-1}; ^1H NMR, δ, 5.62 (dd, 1H, J=6.2 and 1.3) and 5.55 (dd, 1H, J=6.2 and 1.3), 5.45 (dt, 1H, J=1.2 and 7.1) and 5.43 (dt, 1H, J=1.4 and 6.5), 5.06 (apparent d, 1H, J=6.8), 4.91 (m, 1H); 3.96 (m, 1H), 3.72 (s, 3H) and 3.71 (s, 3H), 2.96 (dd, 1H, J=3.2 and 13.8) and 2.81 (dd, 1H, J=7.8 and 11.2) and 2.34 (dd, 1H, J=4.7 and 14.5), 2.10 (dd, 1H, J=8.6 and 13.6), 1.70 (br, 1H), 1.24, (d, 3H, J=6.3), and 1.22 (d, 3H, J=6.4); ^{13}C NMR, δ, 233.3, 141.8 and 141.6, 98.8 and 98.3, 97.9 and 97.5, 93.6 and 93.4, 86.2 and 86.1, 74.7 and 74.4, 68.3

and 67.3, 55.9 and 55.8, 39.7 and 38.7, 23.6 and 23.3; MS m/e 302 (M^+); HRMS m/e for $C_{13}H_{14}CrO_5$ calcd. (M^+) 302.0246, found 302.0233.



[(1,2-Dihydroxyethyl)benzene]tricarbonylchromium (0) (7a)

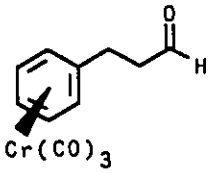
Yellow crystals were obtained in 87% yield; mp 84-86 °C (hexanes); ^{1}H NMR, δ, 5.59 (d, 1H, J=6.3), 5.5-5.43 (m, 4H), 4.49 (dd, 1H, J=7.0, 3.3), 3.82 (dd, 1H, J=11.3, 3.3), 3.66 (dd, 1H, J=11.3, 7.0), 2.66 (br s, 1H), 2.28 (br s, 1H); ^{13}C NMR, δ, 232.6, 111.4, 92.5, 92.4, 92.3, 91.4, 90.1, 72.5, 67.6; MS m/e 274 (M^+); Anal. Calcd. for $C_{11}H_{10}CrO_5$: C, 48.19; H, 3.67. Found: C, 48.17; H, 3.67.

General Procedure. DMSO-TFAA oxidations.

To a solution of DMSO (0.14 mL, 3 equiv) in CH_2Cl_2 at -78°C under nitrogen was added trifluoroacetic anhydride (0.24 mL, 2.5 equiv) over a period of one min. The solution was stirred for 5 min at -78°C, and a solution of **4a** (0.201 g) in CH_2Cl_2 (1 mL) added over a 2 min period. After stirring the reaction mixture for 0.5 h, NEt_3 (0.5 mL) was added, and the solution was allowed to warm to room temperature. Water was added, and the mixture extracted several times with CH_2Cl_2; the combined CH_2Cl_2 layers were dried over $MgSO_4$ and concentrated under reduced pressure. Preparative TLC (1:1 petroleum ether:EtOAc) afforded **4b,** (0.145 g, 72% yield).

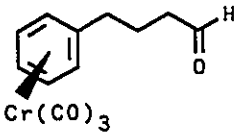
General Procedure. DMSO-SO_3-pyridine oxidations.

To a vigorously stirred solution of 7a (0.1083 g) in DMSO (2 mL) and NEt_3 (0.27 mL, 5 equiv) under nitrogen a 0°C (bath temperature) was added a solution of SO_3-pyridine (0.314 g, 5 equiv) in DMSO (2 mL) over a period of 5 min. The reaction mixture was allowed to stir for 0.5 h, at which time water was added and the mixture subjected a workup identical to that for the DMSO-trifluoroacetic acid procedure. Preparative TLC (1:1 petroleum ether:EtOAc) afforded 7b (0.0871 g, 81% yield).



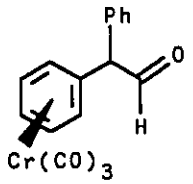
[3-(Oxopropyl)benzene]tricarbonylchromium (0) (1b)

Compound 1b was obtained as a yellow oil; IR (NaCl neat) ν_{max} 1972, 1957, 1869, 1722 cm^{-1}; ^1H NMR, δ, 9.82 (s, 1H), 5.37 (apparent t, 2H, J=6.3), 5.23 (m, 3H), 2.81 (m, 2H), 2.72 (m, 2H); ^{13}C NMR, δ, 233.0, 199.9, 93.8, 93.5, 92.9, 91.0, 44.6, 27.1,; MS m/e 270 (M^+); HRMS m/e calcd. for $C_{12}H_{10}CrO_4$ (M^+) 269.9984, found 269.9980.



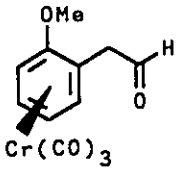
[4-(Oxo)butylbenzene]tricarbonylchromium (0) (2b)

Compound **2b** was obtained as a yellow oil; IR (NaCl neat) ν_{max} 1970, 1958, 1870, 1721 cm^{-1}; ^1H NMR, δ, 9.77 (s, 1H), 5.37 (apparent t, 2H, J=6.4), 5.17 (m, 3H), 2.54 (m, 2H), 2.38 (m, 2H), 1.89 (m, 2H); ^{13}C NMR, δ, 233.1, 201.3, 112.6, 93.9, 92.5, 90.6, 43.0, 34.4, 23.4; MS m/e 284 (M^+); HRMS m/e calcd. for $C_{13}H_{12}CrO_4$ (M^+) 284.0141, found 284.0142.



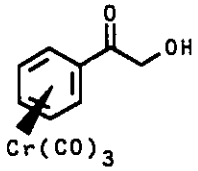
[(2-Oxo-1-phenylethyl)benzene]tricarbonylchromium (0) (3b)

Compound **3b** was obtained as a yellow oil; IR (NaCl neat) ν_{max} 1963, 1871, 1724 cm^{-1}; ^1H NMR, δ, 9.89 (d, 1H, J=0.8), 7.45 (m. 2H), 7.31 (m, 3H), 5.43 (d, 1H, J=6.1), 5.35 (m, 2H), 5.24 (apparent dt, 1H, J=1.3, 6.3), 4.97 (d, 1H, J= 6.4), 4.68 (d, 1H, J=0.8); ^{13}C NMR, δ, 232.3, 196.3, 132.8, 129.8, 129.4, 128.7, 105.8, 94.6, 93.9, 93.0, 91.5, 91.4, 61.6; MS m/e 332 (M^+); HRMS m/e for $C_{17}H_{12}CrO_4$ calcd. (M^+) 332.0141, found, 332.0154.



[1-(2-Oxopropyl)-2-methoxybenzene]tricarbonylchromium (0) (4b)

Compound **4b** was obtained as yellow crystals; mp 117-119 °C (petroleum ether/ether); IR (KBr pellet) ν_{max} 1947, 1865, 1715 cm^{-1}; ^1H NMR, δ, 5.48 (apparent t, 1H, J=6.6), 5.43 (d, 1H, J=6.1), 5.07 (d, 1H, J=6.8), 4.91 (apparent t, 1H, J=6.2), 3.94 (d, 1H, J=17.3), 3.67 (s, 3H), 3.15 (d, 1H, J=17.3), 2.21 (s, 3H); ^{13}C NMR, δ, 233.3, 204.5, 141.6, 97.6, 93.9, 93.8, 86.2, 74.8, 56.1, 44.4, 29.9; MS m/e 300 (M^+); HRMS m/e for $C_{13}H_{12}CrO_5$ calcd. (M^+) 300.0090, found 300.0089.



[(2-Hydroxy-1-oxoethyl)benzene]tricarbonylchromium (0) (7b)

Compound **7b** was obtained as yellow crystals; mp 74-76 °C (hexanes/ether); IR (NaCl neat) ν_{max} 3250 (br), 1972, 1890, 1685 cm^{-1}; ^1H NMR, δ, 6.05 (d, 2H, J=6.3), 5.71 (apparent t, 1H, J=6.2), 5.28 (apparent t, 2H, J=6.5), 4.70 (d, 2H, J=4.7), 3.26 (t, 1H, J=4.7); ^{13}C NMR, δ, 229.8, 196.2, 95.7, 93.3, 90.8, 88.7, 64.4; MS m/e 272 (M^+); Anal. Calcd. for $C_{11}H_8CrO_5$: C, 48.54; H, 2.96. Found: C, 48.29; H, 3.00.

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But I fear that I have already wandered into many details that will have but slender interest for the reader, whose eyes perhaps may never have followed a flight of bees; or who may have regarded them only with the passing interest with which we are all of us apt to regard the flower, the bird or the precious stone , asking of these no more than a slight superficial assurance, and forgetting that the most trivial secret of the non-human object we behold in nature connects more closely perhaps with the profound enigma of our origin and our end, than the secret of those of our passions that we study the most eagerly and the most passionately.

- Maurice Maeterlinck, *The Life of the Bee*